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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 17:28:26 ON 17 MAY 2010

=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY     SESSION
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DICTIONARY FILE UPDATES:  16 MAY 2010  HIGHEST RN 1224049-79-9

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=>
Uploading C:\Program Files\Stnexp\Queries\10595307.str
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chain nodes :
11  26
ring nodes :
1  2  3  4  5  6  7  8  9  10  12  13  14  15  16  17  18  19  20  21  22  23
chain bonds :
8-26  10-11  11-12
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  5-7  6-10  7-8  8-9  9-10  12-13  12-17  13-14  14-15
 15-16  16-17  18-19  18-23  19-20  20-21  21-22  22-23
exact/norm bonds :
8-26  10-11  11-12  18-23  22-23
exact bonds :
18-19  19-20  20-21  21-22
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  5-7  6-10  7-8  8-9  9-10  12-13  12-17  13-14  14-15
 15-16  16-17

G1:H,Ak,Cb,[*1]

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:CLASS  12:Atom  13:Atom  14:Atom  15:Atom  16:Atom  17:Atom  18:Atom  19:Atom
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L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1              STR
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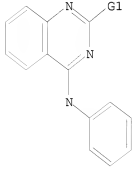


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G1 H,Ak,Cb,[@1]
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Structure attributes must be viewed using STN Express query preparation.

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=> s l1 full
FULL SEARCH INITIATED 17:29:15 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    81008 TO ITERATE

100.0% PROCESSED    81008 ITERATIONS                          59611 ANSWERS
SEARCH TIME: 00.00.11

L2        59611 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                             192.03     192.25

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FILE COVERS 1907 - 17 May 2010  VOL 152 ISS 21
FILE LAST UPDATED: 16 May 2010  (20100516/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Apr 2010
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Feb 2010

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2010.

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s l2
L3         5362 L2

=> s l3 not py>2002
     9845812 PY>2002
L4         495 L3 NOT PY>2002

=> s l4 and ((protein kinase) or antiviral or infectio?)
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       380569 KINASE
       161593 PROTEIN KINASE
                (PROTEIN(W)KINASE)
        80951 ANTIVIRAL
       451622 INFECTIO?
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L5 40 L4 AND ((PROTEIN KINASE) OR ANTIVIRAL OR INFECTIO?)

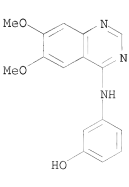
=> d l5 1- ibib abs hitstr
YOU HAVE REQUESTED DATA FROM 40 ANSWERS - CONTINUE? Y/(N):y

L5 ANSWER 1 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2009:905941 CAPLUS
TITLE: Molecular docking study on anticancer activity of plant-derived natural products
AUTHOR(S): Phosrithong, Narumol; Ungwitayatorn, Jiraporn
CORPORATE SOURCE: Faculty of Pharmacy, Mahidol University, Bangkok, 10400, Thailand
SOURCE: Medicinal Chemistry Research No pp. yet given
CODEN: MCREEB; ISSN: 1054-2523
PUBLISHER: Birkhaeuser Boston
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A variety of compds. from plant sources have been reported to possess substantial anticancer properties; however, their modes of action have not been clearly defined. Selected plant-derived compds. that exhibit anticancer activity were subjected to docking simulations using AutoDock 3.0.5. To preliminarily investigate the potential mol. targets and to confirm the exptl. activity testing for these anticancer compds., the docking was performed using different enzymes and receptor proteins involved with cell cycle, cell growth, and DNA replication, i.e., cyclin-dependent protein kinase 2 (CDK-2), CDK-6, DNA topoisomerases I and II, B-cell lymphoma 2 (Bcl-2), vascular endothelial growth factor receptor 2 (VEGFR-2), and the telomere: G-quadruplexes. The docking results revealed that lupeol exhibited better binding interaction to CDK-2 and Bcl-2 than the known CDK-2 and Bcl-2 inhibitors. Epigallocatechin gallate (EGCG) was found to bind to CDK-6 with tighter interaction than several reported CDK-6 inhibitors. Flavopiridol, a synthetic flavonoid, was best bound to DNA topoisomerase I. Green tea catechin was best docked with topoisomerase II and VEGFR-2 and quercetin showed very good binding interaction with telomere: G-quadruplex. The exptl.-derived inhibition constant (Ki) against Bcl-2 and Ki calculated from docking energy were well correlated. Therefore, the calculated Ki could be used as a preliminary tool for screening of Bcl-2 inhibitors before performing exptl. activity assay.

IT 211555-08-7
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mol. docking study on anticancer activity of plant-derived natural products)

RN 211555-08-7 CAPLUS
CN Phenol, 3-[(6,7-dimethoxy-4-quinazolinyl)amino]- (CA INDEX NAME)

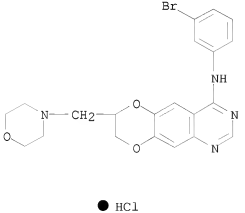


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2003:315030 CAPLUS
DOCUMENT NUMBER: 139:207072
TITLE: 7-substituted-[1,4]dioxano[2,3-g]quinazolines as inhibitors of epidermal growth factor receptor kinase
AUTHOR(S): Lee, Jae Yeol; Park, Yong Kyu; Seo, Seon Hee; Yang, Beom-Seok; Park, Hokoon; Lee, Yong Sup
CORPORATE SOURCE: Medicinal Chemistry Research Center, Korea Institute of Science and Technology, Seoul, 130-650, S. Korea
SOURCE: Archiv der Pharmazie (Weinheim, Germany) (2002), 335(10), 487-494
CODEN: ARPMAS; ISSN: 0365-6233
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:207072

AB With the aim of developing inhibitors of EGFR tyrosine kinase, the 7-methoxymethyl-[1,4]dioxano[2,3-g]quinazolines and 7-mono- or di-alkylaminomethyl-[1,4]dioxano[2,3-g]quinazolines were prepared and evaluated for the inhibition of EGFR tyrosine kinase and the growth inhibition of human tumor cell lines. Some compds. showed potencies against both EGFR tyrosine and the A431 cell line similar to that of PD 153035 with greater aqueous solubilities of their HCl salts.

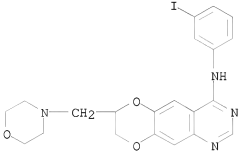
IT 489453-71-6P
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(7-substituted-[1,4]dioxano[2,3-g]quinazolines as inhibitors of epidermal growth factor receptor kinase)
RN 489453-71-6 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazolin-4-amine, N-(3-bromophenyl)-7,8-dihydro-7-(4-morpholinylmethyl)-, hydrochloride (1:1) (CA INDEX NAME)



IT 489453-70-5P 489453-72-7P 489453-73-8P
489453-74-9P 489453-75-0P 489453-77-2P

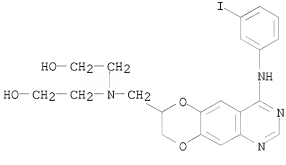
587870-34-6P 587870-35-7P
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(7-substituted-[1,4]dioxano[2,3-g]quinazolines as inhibitors of epidermal growth factor receptor kinase)

RN 489453-70-5 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazolin-4-amine, 7,8-dihydro-N-(3-iodophenyl)-7-(4-morpholinylmethyl)-, hydrochloride (1:1) (CA INDEX NAME)



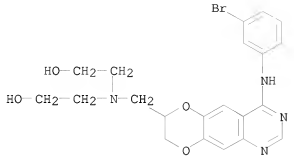
● HCl

RN 489453-72-7 CAPLUS
CN Ethanol, 2,2'-[[[7,8-dihydro-4-[(3-iodophenyl)amino][1,4]dioxino[2,3-g]quinazolin-7-yl]methyl]imino]bis-, monohydrochloride (9CI) (CA INDEX NAME)



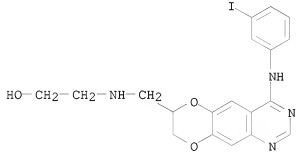
● HCl

RN 489453-73-8 CAPLUS
CN Ethanol, 2,2'-[[[4-[(3-bromophenyl)amino]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]methyl]imino]bis-, monohydrochloride (9CI) (CA INDEX NAME)



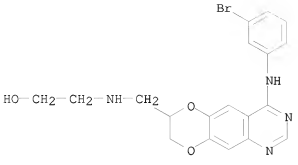
● HCl

RN 489453-74-9 CAPLUS
CN Ethanol, 2-[[[7,8-dihydro-4-[(3-iodophenyl)amino][1,4]dioxino[2,3-g]quinazolin-7-yl]methyl]amino]-, hydrochloride (1:1) (CA INDEX NAME)



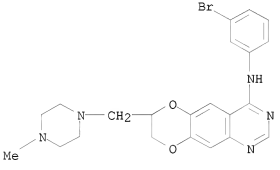
● HCl

RN 489453-75-0 CAPLUS
CN Ethanol, 2-[[[4-[(3-bromophenyl)amino]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]methyl]amino]-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

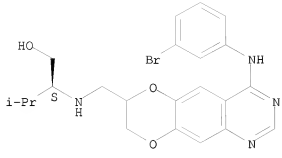
RN 489453-77-2 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazolin-4-amine,
N-(3-bromophenyl)-7,8-dihydro-7-[(4-methyl-1-piperazinyl)methyl]-,
hydrochloride (1:1) (CA INDEX NAME)



● HCl

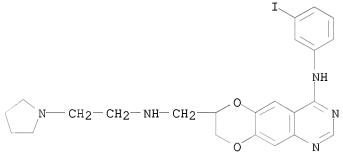
RN 587870-34-6 CAPLUS
CN 1-Butanol, 2-[[[4-[(3-bromophenyl)amino]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]methyl]amino]-3-methyl-, hydrochloride (1:1), (2S)- (CA INDEX NAME)

Absolute stereochemistry.



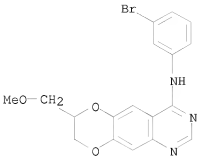
● HCl

RN 587870-35-7 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazoline-7-methanamine,
7,8-dihydro-4-[(3-iodophenyl)amino]-N-[2-(1-pyrrolidinyl)ethyl]-,
hydrochloride (1:1) (CA INDEX NAME)

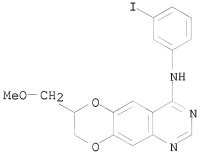


● HCl

IT 489453-49-8P 489453-50-1P
RL: PAC (Pharmacological activity); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(7-substituted-[1,4]dioxano[2,3-g]quinazolines as inhibitors of epidermal growth factor receptor kinase)
RN 489453-49-8 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazolin-4-amine,
N-(3-bromophenyl)-7,8-dihydro-7-(methoxymethyl)- (CA INDEX NAME)



RN 489453-50-1 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazolin-4-amine,
7,8-dihydro-N-(3-iodophenyl)-7-(methoxymethyl)- (CA INDEX NAME)



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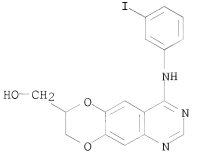
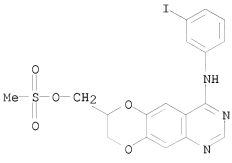
489453-65-8P 489453-66-9P 489453-67-0P
489453-68-1P 587870-31-3P 587870-32-4P
587870-33-5P
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(7-substituted-[1,4]dioxano[2,3-g]quinazolines as inhibitors of epidermal growth factor receptor kinase)
RN 489453-59-0 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazoline-7-methanol,
7,8-dihydro-4-[(3-iodophenyl)amino]- (CA INDEX NAME)

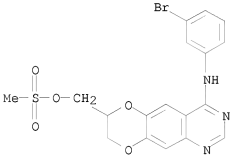


RN 489453-60-3 CAPLUS

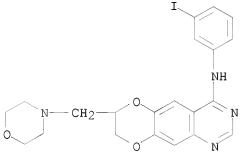
CN [1,4]Dioxino[2,3-g]quinazoline-7-methanol,
7,8-dihydro-4-[(3-iodophenyl)amino]-, 7-methanesulfonate (CA INDEX NAME)



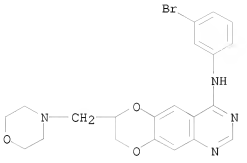
RN 489453-61-4 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazoline-7-methanol,
4-[(3-bromophenyl)amino]-7,8-dihydro-, 7-methanesulfonate (CA INDEX NAME)



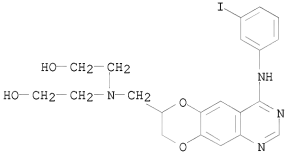
RN 489453-62-5 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazolin-4-amine,
7,8-dihydro-N-(3-iodophenyl)-7-(4-morpholinylmethyl)- (CA INDEX NAME)



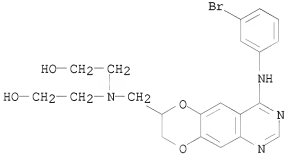
RN 489453-63-6 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazolin-4-amine,
N-(3-bromophenyl)-7,8-dihydro-7-(4-morpholinylmethyl)- (CA INDEX NAME)



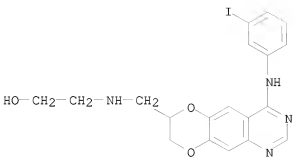
RN 489453-64-7 CAPLUS
CN Ethanol, 2,2'-[[[7,8-dihydro-4-[(3-iodophenyl)amino][1,4]dioxino[2,3-g]quinazolin-7-yl]methyl]imino]bis- (9CI) (CA INDEX NAME)



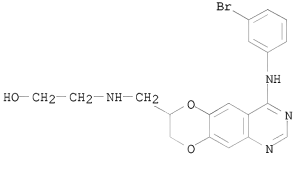
RN 489453-65-8 CAPLUS
CN Ethanol, 2,2'-[[[4-[(3-bromophenyl)amino]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]methyl]imino]bis- (9CI) (CA INDEX NAME)



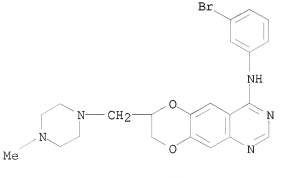
RN 489453-66-9 CAPLUS
CN Ethanol, 2-[[[7,8-dihydro-4-[(3-iodophenyl)amino][1,4]dioxino[2,3-g]quinazolin-7-yl]methyl]amino]- (CA INDEX NAME)



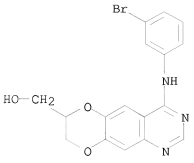
RN 489453-67-0 CAPLUS
CN Ethanol, 2-[[[4-[(3-bromophenyl)amino]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]methyl]amino]- (CA INDEX NAME)



RN 489453-68-1 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazolin-4-amine, N-(3-bromophenyl)-7,8-dihydro-7-[(4-methyl-1-piperazinyl)methyl]- (CA INDEX NAME)

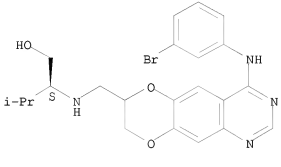


RN 587870-31-3 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazoline-7-methanol, 4-[(3-bromophenyl)amino]-7,8-dihydro- (CA INDEX NAME)

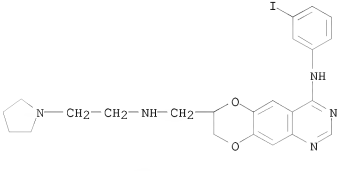


RN 587870-32-4 CAPLUS
CN 1-Butanol, 2-[[[4-[(3-bromophenyl)amino]-7,8-dihydro[1,4]dioxino[2,3-g]quinazolin-7-yl]methyl]amino]-3-methyl-, (2S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 587870-33-5 CAPLUS
CN [1,4]Dioxino[2,3-g]quinazoline-7-methanamine, 7,8-dihydro-4-[(3-iodophenyl)amino]-N-[2-(1-pyrrolidinyl)ethyl]- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2003:57578 CAPLUS
DOCUMENT NUMBER: 139:46544

TITLE: Effects of the epidermal growth factor receptor inhibitor OSI-774, tarceva, on downstream signaling pathways and apoptosis in human pancreatic adenocarcinoma

AUTHOR(S): Ng, Sylvia S. W.; Tsao, Ming-Sound; Nicklee, Trudey; Hedley, David W.

CORPORATE SOURCE: Divisions of Experimental Therapeutics, Ontario Cancer Institute, Medical Biophysics, Princess Margaret Hospital and University of Toronto, Toronto, ON, M5G 2M9, Can.

SOURCE: Molecular Cancer Therapeutics (2002), 1(10), 777-783
CODEN: MCTOCF; ISSN: 1535-7163

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

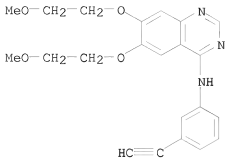
LANGUAGE: English

AB Pancreatic cancer is the fifth leading cause of cancer death in North America. Gemcitabine improves the quality of life of patients but fails to significantly reduce mortality. Our laboratory has demonstrated previously that the phosphatidylinositol 3'-kinase inhibitor wortmannin promotes gemcitabine antitumor. The present study examined the effects of the epidermal growth factor receptor (EGFR) inhibitor OSI-774 ("Tarceva") alone and in combination with wortmannin and/or gemcitabine on downstream signaling mols., as well as apoptosis in primary pancreatic cancer xenografts implanted orthotopicaly in severely combined immunodeficient mice. Tumors established from two pancreatic cancer patients [Ontario Cancer Institute Pancreas number (OCIP#) 2 and OCIP#7] were treated with various combinations of the above three drugs and harvested for analyses of the following: the levels of phosphorylated and nonphosphorylated forms of EGFR, protein kinase B (PKB/Akt) and extracellular-regulated kinase (ERK1/2), and the extent of apoptosis using immunofluorescence image anal. and TUNEL assay, resp. OSI-774 alone significantly inhibited phosphorylation of EGFR in both of the primary xenografts. Phosphorylation of pERK decreased in OCIP#2, but not in OCIP#7. No significant effects on pPKB because of OSI-774 were observed in either tumor type. The extent of apoptosis was significantly increased by 2-fold in OCIP#2 tumors treated with gemcitabine and wortmannin in combination; an addnl. 2-fold increase in apoptosis was evident in the presence of OSI-774. Although wortmannin failed to enhance gemcitabine-induced apoptosis in OCIP#7 tumors, the extent of apoptosis was significantly increased with the inclusion of OSI-774 in the combination. Taken together, these findings support the use of OSI-774 plus a phosphatidylinositol 3'-kinase inhibitor in combination with gemcitabine in the treatment of pancreatic cancer.

IT 183319-69-9, OSI-774
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of epidermal growth factor receptor inhibitor OSI-774, tarceva, on downstream signaling pathways and apoptosis in human pancreatic adenocarcinoma)

RN 183319-69-9 CAPLUS

CN 4-Quinazolinamine, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-, hydrochloride (1:1) (CA INDEX NAME)



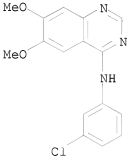
● HCl

OS.CITING REF COUNT: 70 THERE ARE 70 CAPLUS RECORDS THAT CITE THIS RECORD (70 CITINGS)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:887601 CAPLUS
DOCUMENT NUMBER: 138:134956
TITLE: Lyn- and ERK-mediated vs. Ca2+-mediated neutrophil O2- responses with thermal injury
AUTHOR(S): Fazal, Nadeem; Al-Ghoul, Walid M.; Schmidt, Megan J.; Choudhry, Mashkoor A.; Sayeed, Mohammed M.
CORPORATE SOURCE: Burn & Shock Trauma Institute, Department of Surgery, Stritch School of Medicine, Loyola University Chicago, Maywood, IL, 60153, USA
SOURCE: American Journal of Physiology (2002), 283(5, Pt. 1), C1469-C1479
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We evaluated the dependency of neutrophil O2- production on PTK-Lyn and MAPK-ERK1/2 in rats after thermal injury. Activation of PTK-Lyn was assessed by immunopptn. Phosphorylation of ERK1/2 was assessed by Western blot anal. O2- production was measured by isoluminol-enhanced luminometry. Imaging technique was employed to measure neutrophil [Ca2+]i in individual cells. Thermal injury caused marked upregulation of Lyn and ERK1/2 accompanying enhanced neutrophil O2- production Treatment of rats with PTK blocker (AG556) or MAPK blocker (AG1478) before burn injury caused complete inhibition of the resp. kinase activation. Both AG556 and AG1478 produced an .apprx.66% inhibition in O2- production Treatment with diltiazem (DZ) produced an .apprx.37% inhibition of O2- production without affecting Lyn or ERK1/2 activation with burn injury. Ca2+ mobilization was upregulated with burn injury but not affected by treatment of burn rats with AG556. Unlike the partial inhibition of burn-induced O2- production by AG556, AG1478, or DZ, platelet-activating factor antagonist (PAFa) treatment of burn rats produced near complete inhibition of O2- production PAFa treatment also blocked activation of Lyn. The findings suggest that the near complete inhibition of O2- production by PAFa was a result of blockade of PTK as well as Ca2+ signaling. Overall, our studies show that enhanced neutrophil O2- production after thermal injury is a result of potentiation of Ca2+-linked and -independent signaling triggered by inflammatory agents such as PAF.

IT 153436-53-4, AG1478
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mitogen-activated protein Kinase blocker; both
AG556 and AG1478 produced an .apprx.66% inhibition in O2- production)
RN 153436-53-4 CAPLUS
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

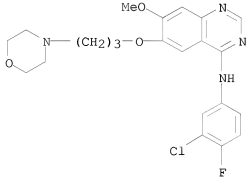
L5 ANSWER 5 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:856249 CAPLUS
DOCUMENT NUMBER: 138:381413
TITLE: Enhancement of antitumor activity of ionizing radiation by combined treatment with the selective epidermal growth factor receptor-tyrosine kinase inhibitor ZD1839 (Iressa)
AUTHOR(S): Bianco, Cataldo; Tortora, Giampaolo; Bianco, Roberto; Caputo, Roberta; Veneziani, Bianca Maria; Caputo, Rosa; Damiano, Vincenzo; Troiani, Teresa; Fontanini, Gabriella; Raben, David; Pepe, Stefano; Bianco, A. Raffaele; Ciardiello, Fortunato
CORPORATE SOURCE: Cattedra di Oncologia Medica, Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita degli Studi di Napoli "Federico II", Naples, 80131, Italy
SOURCE: Clinical Cancer Research (2002), 8(10), 3250-3258
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purpose: The epidermal growth factor receptor (EGFR) is expressed in the majority of human epithelial cancers and has been implicated in the development of cancer cell resistance to cytotoxic drugs and to ionizing radiation. Exptl. Design: We used ZD1839, a selective small mol. EGFR tyrosine kinase inhibitor currently in clin. development. We tested the antiproliferative and the proapoptotic activity of ZD1839 in combination with ionizing radiation in human colon (GEO), ovarian (OVCAR-3), non-small cell lung (A549 and Calu-6), and breast (MCF-7 ADR) cancer cell lines. The antitumor activity of this combination was also tested in nude mice bearing established GEO colon cancer xenografts. Results: With ionizing radiation or ZD1839, a dose-dependent growth inhibition was observed in all of the cancer cell lines growing in soft agar. A cooperative anti-proliferative and proapoptotic effect was obtained when cancer cells

were treated with ionizing radiation followed by ZD1839. This effect was accompanied by inhibition in the expression of the antiapoptotic proteins bcl-xL and bcl-2, and by a suppression of the activated (phosphorylated) form of akt protein. Treatment of mice bearing established human GEO colon cancer xenografts with radiotherapy (RT) resulted in a dose-dependent tumor growth inhibition that was reversible upon treatment cessation. Long term GEO tumor growth regressions were obtained after RT in combination with ZD1839. This resulted in a significant improvement in survival of these mice as compared with the control group ($P < 0.001$); the RT-treated group ($P < 0.001$), or the ZD1839-treated group ($P < 0.001$). The only mice alive 10 wk after tumor cell injection were in the RT-plus-ZD1839 group. Furthermore, 10% of mice in this group were alive and tumor-free after 26 wk. Similar results were obtained in mice bearing established human A549 lung adenocarcinoma xenografts. Finally, the combined treatment with RT plus ZD1839 was accompanied by a significant potentiation in the inhibition of transforming growth factor α, vascular epidermal growth factor, and basic fibroblast growth factor expression in cancer cells, which resulted in significant antiangiogenic effects as determined by immunohistochem. count of neovessels within the GEO tumors. Conclusion: This study provides a rationale for evaluating in cancer patients the combination of ionizing radiation and selective EGFR tyrosine kinase inhibitors such as ZD1839.

IT 184475-35-2, ZD1839
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhancement of antitumor activity of ionizing radiation by combined treatment with selective epidermal growth factor receptor-tyrosine kinase inhibitor ZD1839 (Iressa))

RN 184475-35-2 CAPLUS

CN 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 117 THERE ARE 117 CAPLUS RECORDS THAT CITE THIS RECORD (117 CITINGS)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2002:750038 CAPLUS

DOCUMENT NUMBER: 138:248096

TITLE: Kinase inhibitors impair the effect of estradiol on Ishikawa endometrial adenocarcinoma cells

AUTHOR(S): Treeck, O.; Diedrich, K.; Ortmann, O.

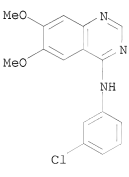
CORPORATE SOURCE: Klinik fuer Frauenheilkunde und Geburtshilfe,

Universitaetsklinikum Luebeck, Luebeck, 23538, Germany
SOURCE: Geburtshilfe und Frauenheilkunde (2002), 62(9), 877-881
CODEN: GEFRA2; ISSN: 0016-5751
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: German

AB Purpose: Interactions between signal transduction cascades involving Tyr kinase and its receptor and the cellular response to stimulation with estradiol have received a great deal of study. The authors studied the effect of inhibitors of receptor Tyr kinases and cytoplasmatic kinases on the cellular response to estradiol in an endometrial adenocarcinoma cell line that expresses estrogen receptors-alpha. Material and Methods: Estrogen effects were measured with a transient reporter gene assay. Ishikawa endometrial adenocarcinoma cells were cultured without serum and transfected with the vector pERE-TA-SEAP via lipofectamines. The vector contains the secreted alkaline phosphatase (SEAP) reporter gene under the control of an estrogen response element (ERE). After transfection the cells were treated with estradiol, the EGFR inhibitor AG1478, and the MEK inhibitors PD98059 and U0126 for 48 h. The activity of the EREs was quantified with luminometric measurement of the SEAP concentration in the culture supernatant. Cellular proliferation was measured with an ELISA that quantified the uptake of BrDU into replicating DNA. Results: Physiol. estradiol stimuli caused activation of the ERE. Simultaneous treatment with the EGFR inhibitor AG1478 significantly increased the estradiol-induced activation of ERE. In contrast, both MEK inhibitors reduced both ERE activation and estradiol-induced cellular proliferation. Conclusion: Treatment with the EGFR inhibitor AG1478 increased the response of endometrial adenocarcinoma cells to estrogen stimuli. MEK inhibitors can block MAP kinase signal transduction and inhibit cellular estradiol effects. This suggests that inhibitors of cytoplasmatic kinases may be more useful than EGFR inhibitors in the treatment of endometrial cancers that express estrogen receptors.

IT 153436-53-4, AG1478
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kinase inhibitors on effect of estradiol on endometrial adenocarcinoma)

RN 153436-53-4 CAPLUS
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



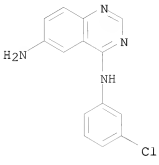
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACCESSION NUMBER: 2002:749928 CAPLUS
DOCUMENT NUMBER: 138:378677
TITLE: Inhibition of epidermal growth factor receptor-mediated signaling by "Combi-Triazene" BJ2000, a new probe for Combi-Targeting postulates
AUTHOR(S): Brahimi, Fouad; Matheson, Stephanie L.; Dudouit, Fabienne; McNamee, James P.; Tari, Ana M.; Jean-Claude, Bertrand J.
CORPORATE SOURCE: Cancer Drug Research Laboratory, Department of Medicine, Division of Medical Oncology, McGill University Health Center/Royal Victoria Hospital, Montreal, QC, Can.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2002), 303(1), 238-246
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

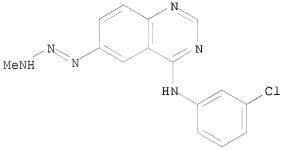
AB The Combi-Targeting concept postulates that a mol. termed combi-mol. (C-mol.) with binary epidermal growth factor receptor (EGFR) targeting/DNA-damaging properties and with the ability to be hydrolyzed to another EGFR inhibitor should induce sustained antiproliferative activity in cells overexpressing EGFR. Because we postulate that the EGFR affinity of the C-mol. and that of its hydrolytic metabolites are critical parameters for sustained potency against EGFR-overexpressing cells, we synthesized BJ2000 (IC50 = 0.1 μM, competitive binding at ATP site), a novel C-mol. that can decompose into a 6-amino-4-anilinoquinazoline FD105 (IC50 = 0.2 μM). Studies using the EGFR-overexpressing A431 cells revealed that BJ2000 could damage DNA and block epidermal growth factor-stimulated EGFR autophosphorylation by a partially irreversible mechanism. Blockade of EGFR autophosphorylation subsequently induced inhibition of mitogen-activated protein kinase activation and c-fos gene expression. ELISA and growth factor-mediated stimulation of proliferation assays in the EGFR-expressing NIH3T3HER14 demonstrated the preferential EGFR-targeting properties of BJ2000, and more importantly suggest that blockade of EGFR phosphorylation by this drug translate into significant growth inhibitory effects. These properties culminated into irreversible antiproliferative effects as confirmed by a sulforhodamine B assay. Five days after a 2-h treatment, BJ2000 retained significant antiproliferative effect in A431 cells, whereas its reversible metabolite FD105 almost completely lost its activity. This result in toto lend support to the Combi-Targeting concept according to which a mol. conjugate kept small enough to interact with EGFR and designed to degrade into another inhibitor of the same target plus a DNA-damaging species may induce sustained growth inhibitory effect in EGFR-overexpressing cells.

IT 153436-71-6, FD 105
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrolysis of BJ2000 to a 6-amino-4-anilinoquinazoline EGFR inhibitor; inhibition of EGF receptor-mediated signaling by "Combi-Triazene" BJ2000, a cytotoxic compound with binary EGF receptor targeting/DNA-damaging properties)

RN 153436-71-6 CAPLUS
CN 4,6-Quinazolinediamine, N4-(3-chlorophenyl)- (CA INDEX NAME)



IT 454691-39-5, BJ 2000
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of EGF receptor-mediated signaling by "Combi-Triazene" BJ2000, a cytotoxic compound with binary EGF receptor targeting/DNA-damaging properties)
RN 454691-39-5 CAPLUS
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6-(3-methyl-2-triazen-1-yl)- (CA INDEX NAME)



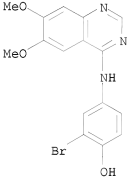
OS.CITING REF COUNT: 28 THERE ARE 28 CAPLUS RECORDS THAT CITE THIS RECORD (28 CITINGS)
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:694236 CAPLUS
DOCUMENT NUMBER: 138:248178
TITLE: Augmentation of mast cell bactericidal activity by the anti-leukemic drug, 4-(3'-bromo-4'-hydroxylphenyl)amino-6,7-dimethoxyquinazoline
AUTHOR(S): Malaviya, Ravi; Navara, Christopher; Uckun, Fatih M.
CORPORATE SOURCE: Department of Allergy and Inflammatory Diseases, Parker Hughes Cancer Center, St. Paul, MN, 55113, USA
SOURCE: Leukemia & Lymphoma (2002), 43(6), 1329-1332
CODEN: LELYEA; ISSN: 1042-8194
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mast cells play a pivotal role in host innate immune defense against gram neg. bacterial infections by killing gram neg. bacteria and

recruiting neutrophils to the sites of active infection through the release of TNFα and leukotrienes. Here, we report that the antileukemic compound 4-(3'-bromo-4'-hydroxylphenyl)amino-6,7-dimethoxyquinazoline, designated as MASTPROM, augments the bactericidal activity of mast cells by increasing the binding of bacteria to and their phagocytosis by mast cells. MASTPROM also promoted the bacterial clearance in a mouse model of bacterial peritonitis. MASTPROM may provide the basis for novel supportive care regimens aimed at augmenting the bactericidal activity of mast cells and thereby potentiating the innate immune response against gram neg. organisms.

IT 211555-04-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(augmentation of mast cell bactericidal activity by the antileukemic drug, (bromohydroxylphenyl)aminodimethoxyquinazoline)

RN 211555-04-3 CAPLUS
CN Phenol, 2-bromo-4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

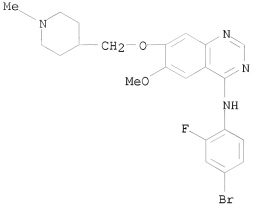
L5 ANSWER 9 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:640221 CAPLUS
DOCUMENT NUMBER: 138:198255
TITLE: ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration
AUTHOR(S): Wedge, Stephen R.; Ogilvie, Donald J.; Dukes, Michael; Kendrew, Jane; Chester, Rosemary; Jackson, Janet A.; Boffey, Sarah J.; Valentine, Paula J.; Curwen, Jon O.; Musgrove, Helen L.; Graham, George A.; Hughes, Gareth D.; Thomas, Andrew P.; Stokes, Elaine S. E.; Curry, Brenda; Richmond, Graham H. P.; Wadsworth, Peter F.; Bigley, Alison L.; Hennequin, Laurent F.
CORPORATE SOURCE: Departments of Cancer and Infection Research, AstraZeneca, Cheshire, SK10 4TG, UK
SOURCE: Cancer Research (2002), 62(16), 4645-4655
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB ZD6474 [N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-

yl)methoxy]quinazolin-4-amine] is a potent, p.o. active, low mol. weight inhibitor of kinase insert domain-containing receptor [KDR/vascular endothelial growth factor receptor (VEGFR) 2] tyrosine kinase activity (IC50 = 40 nM). This compound has some addnl. activity vs. the tyrosine kinase activity of fms-like tyrosine kinase 4 (VEGFR3; IC50 = 110 nM) and epidermal growth factor receptor (EGFR/HER1; IC50 = 500 nM) and yet demonstrates selectivity against a range of other tyrosine and serine-threonine kinases. The activity of ZD6474 vs. KDR tyrosine kinase translates into potent inhibition of vascular endothelial growth factor-A (VEGF)-stimulated endothelial cell (human umbilical vein endothelial cell) proliferation in vitro (IC50 = 60 nM). Selective inhibition of VEGF signaling has been demonstrated in vivo in a growth factor-induced hypotension model in anesthetized rat: administration of ZD6474 (2.5 mg/kg, i.v.) reversed a hypotensive change induced by VEGF (by 63%) but did not significantly affect that induced by basic fibroblast growth factor. Once-daily oral administration of ZD6474 to growing rats for 14 days produced a dose-dependent increase in the femoro-tibial epiphyseal growth plate zone of hypertrophy, which is consistent with inhibition of VEGF signaling and angiogenesis in vivo. Administration of 50 mg/kg/day ZD6474 (once-daily, p.o.) to athymic mice with intradermally implanted A549 tumor cells also inhibited tumor-induced neovascularization significantly (63% inhibition after 5 days; $P < 0.001$). Oral administration of ZD6474 to athymic mice bearing established (0.15-0.47 cm3), histol. distinct (lung, prostate, breast, ovarian, colon, or vulval) human tumor xenografts or after implantation of aggressive syngeneic rodent tumors (lung, melanoma) in immunocompetent mice, produced a dose-dependent inhibition of tumor growth in all cases. Statistically significant antitumor activity was evident in each model with at least 25 mg/kg ZD6474 once daily ($P < 0.05$, one-tailed t test). Histol. anal. of Calu-6 tumors treated with 50 mg/kg/day ZD6474 for 24 days showed a significant reduction (>70%) in CD31 (endothelial cell) staining in nonnecrotic regions. ZD6474 also restrained growth of much larger (0.9 cm3 volume) Calu-6 lung tumor xenografts and induced profound regression in established PC-3 prostate tumors of 1.4 cm3 volume ZD6474 is currently in Phase I clin. development as a once-daily oral therapy in patients with advanced cancer.

IT 443913-73-3, ZD6474
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration)

RN 443913-73-3 CAPLUS

CN 4-Quinazolinamine, N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 339 THERE ARE 339 CAPLUS RECORDS THAT CITE THIS RECORD (339 CITINGS)
REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:523279 CAPLUS
DOCUMENT NUMBER: 137:242433
TITLE: Vitamin D inhibits the activation of stress-activated protein kinases by physiological and environmental stresses in keratinocytes
AUTHOR(S): Ravid, A.; Rubinstein, E.; Gamady, A.; Rotem, C.; Liberman, U. A.; Koren, R.
CORPORATE SOURCE: Basil and Gerald Felsenstein Medical Research Center, Sackler Faculty of Medicine, Tel Aviv University, Petah Tikva, 49100, Israel
SOURCE: Journal of Endocrinology (2002), 173(3), 525-532
CODEN: JOENAK; ISSN: 0022-0795
PUBLISHER: Society for Endocrinology
DOCUMENT TYPE: Journal
LANGUAGE: English

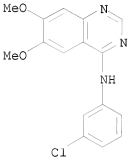
AB In addition to its known effects on keratinocyte proliferation and differentiation, the hormonal form of vitamin D, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), has been shown to protect keratinocytes from UV- and chemotherapy-induced damage. Epidermal keratinocytes contain both the machinery needed to produce 1,25(OH)2D3 and vitamin D receptors. The activation of the stress-activated protein kinases (SAPKs), such as c-Jun N-terminal kinase (JNK) and p38, is an early cellular response to stress signals and an important determinant of cell fate. This study examines whether modulation of these SAPKs is associated with the effects of 1,25(OH)2D3 on keratinocytes under stress. HaCaT keratinocytes were exposed to heat shock, hyperosmotic concns. of sorbitol, the epidermal growth factor receptor tyrosine kinase inhibitor AG1487, the pro-inflammatory cytokine tumor necrosis factor α, and H2O2. These stresses activated both SAPKs. Pretreatment with 1,25(OH)2D3 inhibited the activation of JNK by all stresses and the activation of p38 by heat shock, AG1478 and tumor necrosis factor α. Under the same conditions, treatment with 1,25(OH)2D3 protected HaCaT keratinocytes from cytotoxicity induced by exposure to H2O2 and hyperosmotic shock. The effect of 1,25(OH)2D3 was dose-dependent, already apparent at nanomolar concns., and time-dependent, maximal after a 24-h pre-incubation. We suggest that inhibition of SAPK activation may account for some of the

well-documented protective effects of 1,25(OH)2D3 on epidermal cells during exposure to UV or chemotherapy and may also be related to the anti-inflammatory actions of the hormone in skin.

IT 153436-53-4, Tyrphostin AG 1478
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (stressor; vitamin D inhibits activation of stress-activated protein kinases by physiol. and environmental stresses in keratinocytes)

RN 153436-53-4 CAPLUS

CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 31 THERE ARE 31 CAPLUS RECORDS THAT CITE THIS RECORD (31 CITINGS)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2002:486039 CAPLUS

DOCUMENT NUMBER: 138:66279

TITLE: Influence of epidermal growth factor receptor (EGFR), p53, and intrinsic MAP kinase pathway status of tumour cells on the antiproliferative effect of ZD1839 ('Iressa')

AUTHOR(S): Magne, N.; Fischel, J. L.; Dubreuil, A.; Formento, P.; Poupon, M.-F.; Laurent-Puig, P.; Milano, G.

CORPORATE SOURCE: Department of Oncopharmacology, Centre Antoine Lacassagne, Nice, Fr.

SOURCE: British Journal of Cancer (2002), 86(9), 1518-1523
CODEN: BJCAAI; ISSN: 0007-0920

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

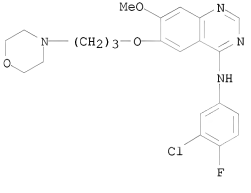
AB ZD1839 ('Iressa') is an orally active, selective epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), which blocks signal transduction pathways implicated in proliferation and survival of cancer cells, and other host-dependent processes promoting cancer growth. Permanent downstream activation of the mitogen-activated protein kinase pathway can theor. bypass the upstream block of epidermal growth factor receptor-dependent mitogen-activated protein kinase activation at the epidermal growth factor receptor level. The authors investigated the impact of epidermal growth factor receptor content, p53 status, and mitogen-activated protein kinase signalling status on ZD1839 sensitivity in a panel of human tumor cell lines: 7 head and neck cancer cell lines and 2 colon cancer cell lines (LoVo, HT29) with derivs. differing only by a specific modification in p53 status (LoVo p53 wt + p53 mut cells, HT29 p53 mut + p53 wt rescued cells). The antiproliferative activity of ZD1839 was

evaluated by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide test ZD1839 concns. ranged from 0.2-200 μm (48 h exposure). Epidermal growth factor receptor expression, p53 status, and p42/p44 (for testing a constitutively active mitogen-activated protein kinase pathway status) were determined by competition anal. (Scatchard plots), denaturing gradient cell electrophoresis and Western blot, resp. Epidermal growth factor receptor levels ranged from 388 to 33794 fmol mg-1 protein, a range that is similar to that found in head and neck tumors. The IC50 values for cell sensitivity to ZD1839 ranged from 6 to 31 μm and a significant inverse correlation between IC50 values and epidermal growth factor receptor levels was observed There was no influence of p53 status on the sensitivity to ZD1839. In 2 head and neck cancer cell lines with comparably elevated epidermal growth factor receptor expression, a 2-fold higher ZD1839 IC50 value was found for the 1 with a constitutively active mitogen-activated protein kinase. In conclusion, ZD1839 was active against cells with a range of epidermal growth factor receptor levels, although more so in cells with higher epidermal growth factor receptor expression. Activity was unaffected by p53 status, but was reduced in cells strongly dependent on epidermal growth factor receptor signalling in the presence of an intrinsically activated mitogen-activated protein kinase pathway.

IT 184475-35-2, Iressa
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiproliferative effect of ZD1839)

RN 184475-35-2 CAPLUS

CN 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 88 THERE ARE 88 CAPLUS RECORDS THAT CITE THIS RECORD (88 CITINGS)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2002:445818 CAPLUS

DOCUMENT NUMBER: 137:212732

TITLE: Inhibitory effect and its kinetic analysis of tryphostin AG1478 on recombinant human protein kinase CK2 holoenzyme

AUTHOR(S): Liu, Xin-Guang; Liang, Nian-Ci

CORPORATE SOURCE: Institute of Biochemistry and Molecular Biology, Guangdong Medical College, Zhanjiang, 524023, Peop. Rep. China

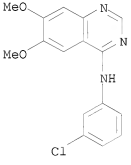
SOURCE: Acta Pharmacologica Sinica (2002), 23(6), 556-561
CODEN: APSCG5; ISSN: 1671-4083
PUBLISHER: Science Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aim: To study the direct effect of tyrphostin AG1478 [4-(3-chloroanilino)-6,7-dimethoxyquinazoline] on recombinant human protein kinase CK2 holoenzyme and its kinetics. Methods: Recombinant human protein kinase CK2 α and β subunits were mixed at equal molar ratio and CK2 holoenzyme were reconstituted. The CK2 activity was assayed by detecting incorporation of [γ-32P]ATP or [γ-32P]GTP into substrates in various conditions. Results: These results demonstrated that the recombinant human CK2 was a second messengers (Ca2+, cAMP, and cGMP)-independent protein kinase, the characterization and function of the reconstituted holoenzyme were consistent with those of native CK2. AG1478 strongly inhibited the holoenzyme activity of recombinant human protein kinase CK2 with IC50 of 25.9 μmol/L, the inhibition is very close to that of N-(2-aminoethyl)-5-chloronaphthalene-1-sulfonamide (A3), but less potent than that of 5, 6-dichloro-1-β-D-ribofuranosylbenzimidazole (DRB), known as CK2 special inhibitors with IC50 of 25.5 μmol/L and 10.4 μmol/L resp. Kinetic studies of AG1478 on recombinant human CK2 showed that inhibitions were competitive with both GTP and casein, thus AG1478 was as bisubstrate inhibitor. Conclusion: The present study indicates that AG1478 is not only an effective inhibitor of protein tyrosine kinases of epidermal growth factor receptor (EGFR), but also a novel potent inhibitor of protein kinase CK2. The recombinant human protein kinase CK2 might be used as a mol. target for simpler screening and development of more effective inhibitors of CK2.

IT 153436-53-4
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human protein kinase CK2 can be inhibited by tryphostin AG1478)

RN 153436-53-4 CAPLUS

CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



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REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

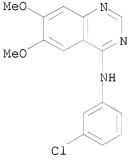
L5 ANSWER 13 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:340575 CAPLUS
DOCUMENT NUMBER: 137:108320

TITLE: Identifying protein kinase inhibitors using an assay based on inhibition of aerial hyphae formation in Streptomyces
AUTHOR(S): Waters, Barbara; Saxena, Geeta; Wanggui, Yangsheng; Kau, David; Wrigley, Stephen; Stokes, Richard; Davies, Julian
CORPORATE SOURCE: Cubist Pharmaceuticals, Inc., Vancouver, BC, V6T 1Z3, Can.
SOURCE: Journal of Antibiotics (2002), 55(4), 407-416
CODEN: JANTAJ; ISSN: 0021-8820
PUBLISHER: Japan Antibiotics Research Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have identified a strain of Streptomyces in which aerial hyphae formation appears to be especially sensitive to inhibition by protein kinase inhibitors. Using this assay, a number of bacterial cultures have been screened and novel inhibitors of eukaryotic protein kinases have been identified. Since M. tuberculosis possesses multiple eukaryotic-like protein kinase genes, we tested the active kinase inhibitors for the inhibition of mycobacterial growth and obtained several potent compds. This identifies a new biochem. class of antimycobacterial agents.

IT 153436-53-4, Ag-1478
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(identifying protein kinase inhibitors using assay based on inhibition of aerial hyphae formation in Streptomyces)

RN 153436-53-4 CAPLUS
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:86818 CAPLUS
DOCUMENT NUMBER: 136:395481
TITLE: Differential sensitivity of cancer cells to inhibitors of the epidermal growth factor receptor family
AUTHOR(S): Bishop, Philippe C.; Myers, Timothy; Robey, Robert; Fry, David W.; Liu, Edison T.; Blagosklonny, Mikhail V.; Bates, Susan E.
CORPORATE SOURCE: Medicine Branch, NCI, NIH, Bethesda, MD, 20892, USA
SOURCE: Oncogene (2002), 21(1), 119-127
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group

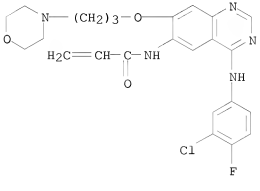
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Clin. responses to the HER1 (EGF receptor) inhibitors and HER2/neu/ErbB2 inhibitors correlate with high levels of receptor expression. However, a significant subset of patients with high receptor levels appear to be refractory to treatment. We have observed similar results in the 60 cell lines of the NCI Anti-Cancer Drug Screen using a panel of 11 selective HER1 inhibitors. As expected, low HER1-expressing cell lines were insensitive to HER1 inhibitors. In cell lines with high HER1 expression, low concns. of HER1 inhibitors potently inhibit both HER1 phosphorylation and the mitogen-activated protein kinase (MAPK) pathway. However, this inhibition did not always correlate with cellular arrest. High HER1-expressing cell lines can be subdivided into two groups based on their sensitivity to HER1 inhibitors. In the sensitive group, receptor and growth inhibition was concordant and occurred at submicromolar concns. of HER1 inhibitors. In the insensitive group, receptor inhibition occurred at a low concentration (< 1 M) but concns. that were ten times or higher were required for growth inhibition. Also, neither induction of p21 and cyclin D1 nor p53 status could explain the difference between sensitive and insensitive cells. Although EGF activated the MAPK pathway in all cell lines, only drug-sensitive cell lines responded to EGF (accelerated entry from G1 to S) and to HER1 inhibitors (G1 arrest) by changes in cell cycling. Furthermore, an EGF-dependent immortalized mammary epithelial cell line was extremely sensitive to a panel of HER1 inhibitors. We infer that independence from mitogen-mediated signaling confers insensitivity to HER1 inhibitors in a large subset of cancer cell lines.

IT 289499-45-2, NSC 709239
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PD 183805; sensitivity of cancer cells to inhibitors of EGF receptor family)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, hydrochloride (1:2) (CA INDEX NAME)

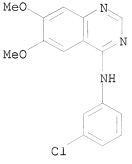


● 2 HCl

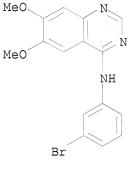
IT 153436-53-4, NSC 693255 153436-54-5, PD 153035
194423-15-9, NSC 691856

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sensitivity of cancer cells to inhibitors of EGF receptor family)

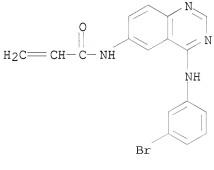
RN 153436-53-4 CAPLUS
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



RN 153436-54-5 CAPLUS
CN 4-Quinazolinamine, N-(3-bromophenyl)-6,7-dimethoxy- (CA INDEX NAME)



RN 194423-15-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-6-quinazolinyl]- (CA INDEX NAME)



OS.CITING REF COUNT: 64 THERE ARE 64 CAPLUS RECORDS THAT CITE THIS RECORD (64 CITINGS)

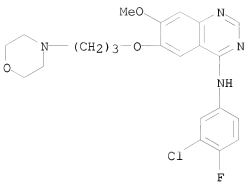
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:75383 CAPLUS
DOCUMENT NUMBER: 137:163415
TITLE: Pharmacodynamic studies of the epidermal growth factor receptor inhibitor ZD1839 in skin from cancer patients: Histopathologic and molecular consequences of receptor inhibition
AUTHOR(S): Albanell, Joan; Rojo, Federico; Averbuch, Steve; Feyereislova, Andrea; Mascaro, Jose Manuel; Herbst, Roy; LoRusso, Patricia; Rischin, Danny; Sauleda, Silvia; Gee, Julia; Nicholson, Robert I.; Baselga, Jose
CORPORATE SOURCE: Oncology Service, Vall d'Hebron University Hospital, Barcelona, 08035, Spain
SOURCE: Journal of Clinical Oncology (2002), 20(1), 110-124
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor ZD1839 (Iressa; Astra-Zeneca Pharmaceuticals, Alderley Park, United Kingdom) is under development as an anticancer agent. We studied the pharmacodynamic effects of ZD1839 on EGFR in the skin, an EGFR-dependent tissue, in cancer patients participating in ZD1839 phase I clin. trials. We studied 104 pre- and/or on-ZD1839 therapy (approx. day 28 of therapy) skin biopsies from 65 patients receiving escalating doses of daily oral ZD1839. We measured ZD1839 effects on EGFR activation by immunohistochem. using an antibody specific for the activated (phosphorylated) EGFR. Effects on receptor signaling (activated mitogen-activated protein kinase [MAPK]), proliferation, p27KIP1, and maturation were also assessed. Histopathol., the stratum corneum of the epidermis was thinner during therapy (P <.001). In hair follicles, prominent keratin plugs and microorganisms were found in dilated infundibula. ZD1839 suppressed EGFR phosphorylation in all EGFR-expressing cells (P <.001). In addition, ZD1839 inhibited MAPK activation (P <.001) and reduced keratinocyte proliferation index (P <.001). Concomitantly, ZD1839 increased the expression of p27KIP1 (P <.001) and maturation markers (P <.001) and increased apoptosis (P <.001). These effects were observed at all dose levels, before reaching dose-limiting toxicities. ZD1839 inhibits EGFR activation and affects downstream receptor-dependent processes in vivo. These effects were profound at doses well below the one producing unacceptable toxicity, a finding that strongly supports pharmacodynamic assessments to select optimal doses instead of a maximum-tolerated dose for definitive efficacy and safety trials.

IT 184475-35-2, ZD1839
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacodynamic studies of the epidermal growth factor receptor inhibitor ZD1839 in skin from cancer patients: histopathol. and mol. consequences of receptor inhibition)

RN 184475-35-2 CAPLUS
CN 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 266 THERE ARE 266 CAPLUS RECORDS THAT CITE THIS RECORD (266 CITINGS)
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:70922 CAPLUS
DOCUMENT NUMBER: 136:363393
TITLE: Insulin-like growth factor receptor I mediates resistance to anti-epidermal growth factor receptor therapy in primary human glioblastoma cells through continued activation of phosphoinositide 3-kinase signaling
AUTHOR(S): Chakravarti, Arnab; Loeffler, Jay S.; Dyson, Nicholas J.
CORPORATE SOURCE: Department of Radiation Oncology, Massachusetts General Hospital/Harvard Medical School, Charlestown, MA, 02129, USA
SOURCE: Cancer Research (2002), 62(1), 200-207
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

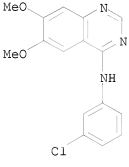
AB Overexpression of the epidermal growth factor receptor (EGFR) has been shown previously to correlate with enhanced malignant potential of many human tumor types, including glioblastoma multiforme (GBM). Anti-EGFR targeting has been demonstrated to enhance apoptosis and reduce both cellular invasion and angiogenic potential. It remains unclear whether absolute EGFR expression levels are sufficient to predict which tumors will respond best to anti-EGFR therapy. The authors have identified two primary GBM cell lines with equivalent EGFR expression levels with very different sensitivities to the EGFR receptor tyrosine kinase inhibitor, AG1478. This was apparent despite similar redns. in EGFR signaling in both cell lines, as measured by phospho-EGFR levels. AG1478 enhanced both spontaneous and radiation-induced apoptosis and reduced invasive potential in the GBMS, but not in the GBMR, cell line. The resistant GBMR cell line demonstrated an up-regulation of insulin-like growth factor receptor I (IGFR-I) levels on AG1478 administration. This resulted in sustained signaling through the phosphoinositide 3-kinase pathway, resulting in potent antiapoptotic and proinvasion effects. Cotargeting IGFR-I with EGFR greatly enhanced both spontaneous and radiation-induced apoptosis of the GBMR cells and reduced their invasive potential. Akt1 and p70s6k appeared to be important downstream targets of IGFR-I-mediated resistance to anti-EGFR targeting. These findings suggest that IGFR-I signaling

through phosphoinositide 3-kinase may represent a novel and potentially important mechanism of resistance to anti-EGFR therapy.

IT 153436-53-4, AG1478
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(insulin-like growth factor receptor I mediates resistance to anti-epidermal growth factor receptor therapy in primary human glioblastoma cells through continued activation of phosphoinositide 3-kinase signaling)

RN 153436-53-4 CAPLUS

CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 206 THERE ARE 206 CAPLUS RECORDS THAT CITE THIS RECORD (210 CITINGS)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 17 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2002:53817 CAPLUS

DOCUMENT NUMBER: 137:118875

TITLE: Inhibition of erbB receptor (HER) tyrosine kinases as a strategy to abrogate antiestrogen resistance in human breast cancer

AUTHOR(S): Kurokawa, Hirokazu; Arteaga, Carlos L.

CORPORATE SOURCE: Departments of Medicine and Cancer Biology and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, 37232, USA

SOURCE: Clinical Cancer Research (2001), 7(12, Suppl.), 4436S-4442S
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal; General Review

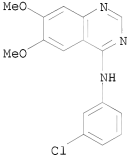
LANGUAGE: English

AB A review. It has been proposed that binding of ligand to the estrogen receptor (ER) releases its association with transcriptional corepressors, allowing the ER to recruit coactivators, which possess histone acetylase activity, and induce transcription of gene promoters containing estrogen response elements. It has also been proposed that the antiestrogen tamoxifen recruits transcriptional corepressors to the AF-2 region of the hormone-binding domain of the ER, thus blocking ER-mediated transcription. The ER cross-talks with a number of mitogenic signaling pathways and second messengers, like the epidermal growth factor receptor, the insulin-like growth factor-1 receptor, mitogen-activated protein (MAP) kinase, phosphatidylinositol-3 kinase/Akt, dopamine, and cAMP. Some of these mols. may: (a) support ligand-independent ER transcription; (b) increase the association of ER with coactivators of transcription; and/or (c) reduce

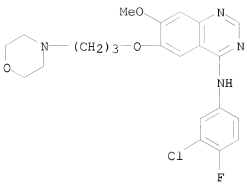
the antiestrogen-induced association of ER with corepressors. These events either alone or in combination may result in hormone independence and/or antiestrogen resistance. The authors have examined whether signaling by HER2/neu (erbB-2) receptor tyrosine kinase, which can induce antiestrogen resistance, can also disrupt the tamoxifen-induced interaction of ER with transcriptional corepressors. Notably, tamoxifen-induced association of ER with the transcriptional corepressors N-CoR or SMRT was reduced in HER2-overexpressing breast tumor cells but not in cells with low HER2 levels. Small mol. inhibitors of the HER2 kinase or MAP extracellular signal-regulated kinase 1/2 or dominant-neg. MAP extracellular signal-regulated kinase 1/2 constructs restored the inhibitory effect of tamoxifen on both ER-mediated transcription and tumor cell proliferation. Treatment with both tamoxifen and the small mol. HER1/2 kinase inhibitor AG1478 reduced mitogen-activated protein kinase activity and markedly reduced growth of established MCF-7/HER2 xenografts in athymic nude mice. Similar results have been obtained with ZD1839 ("Iressa"), an epidermal growth factor receptor (HER1) tyrosine kinase inhibitor. Taken together, these data suggest that exogenous inhibitors of the HER-signaling network and other mitogenic pathways can abrogate or delay the emergence of antiestrogen resistance, thus providing an evaluable therapeutic strategy in human breast carcinoma.

IT 153436-53-4, AG1478 184475-35-2, ZD1839
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of erbB receptor tyrosine kinases signaling as strategy to abrogate antiestrogen resistance in human breast cancer)

RN 153436-53-4 CAPLUS
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



RN 184475-35-2 CAPLUS
CN 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (CA INDEX NAME)

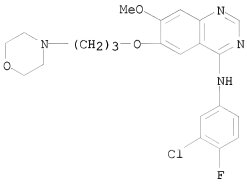


OS.CITING REF COUNT: 30 THERE ARE 30 CAPLUS RECORDS THAT CITE THIS RECORD (30 CITINGS)
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:53804 CAPLUS
DOCUMENT NUMBER: 137:118874
TITLE: Prospects for combining hormonal and nonhormonal growth factor inhibition
AUTHOR(S): Wakeling, Alan E.; Nicholson, Robert I.; Gee, Julia M. W.
CORPORATE SOURCE: Cancer Research Department, AstraZeneca Pharmaceuticals, Cheshire, SK10 4TG, UK
SOURCE: Clinical Cancer Research (2001), 7(12, Suppl.), 4350S-4355S
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with refs. In patients with estrogen receptor (ER)-neg. disease or ER+ hormone-resistant disease, the dominant influence on tumor cell growth is growth factors, e.g., epidermal growth factor (EGF), heregulins, and insulin-like growth factors acting through specific receptor tyrosine kinases at the cell surface. This superfamily of ligand-activated growth factor receptors triggers cascades of biochem. signals that influence tumor cell motility, invasiveness, angiogenesis, and survival, as well as proliferation. In breast tumors, expression of epidermal growth factor receptor (EGFR) and/or erbB2 is associated with poor prognosis; the therapeutic utility of blocking these receptors has been established using trastuzumab (Herceptin), a monoclonal antibody that blocks erbB2 signaling. An alternative therapeutic approach is offered by small mol. inhibitors of EGFR-TK, exemplified by ZD1839 (Iressa), a potent and selective EGFR-TK inhibitor. Resistance to tamoxifen is associated with up-regulation of the EGFR-TK pathway and mitogen-activated protein kinase activity is substantially increased in tamoxifen-resistant MCF-7 cells. ZD1839 treatment of tamoxifen-resistant MCF-7 cells blocks mitogen-activated protein kinase activity. Furthermore, treatment of wild-type MCF-7 cells with tamoxifen and ZD1839 prevents development of tamoxifen resistance. These data support the potential clin. utility of ZD1839 in tamoxifen-resistant breast cancer and suggest the possibility of preventing resistance by the early use of combination ZD1839 with antiestrogenic agents such as tamoxifen or ICI 182,780.

IT 184475-35-2, ZD1839
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prospects for combining hormonal and nonhormonal growth factor inhibition)
RN 184475-35-2 CAPLUS
CN 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

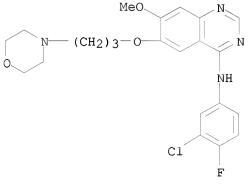
L5 ANSWER 19 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2002:51027 CAPLUS
DOCUMENT NUMBER: 137:119184
TITLE: Oral administration of a novel taxane, an antisense oligonucleotide targeting protein kinase A, and the epidermal growth factor receptor inhibitor Iressa causes cooperative antitumor and antiangiogenic activity
AUTHOR(S): Tortora, Giampaolo; Caputo, Rosa; Damiano, Vincenzo; Fontanini, Gabriella; Melisi, Davide; Veneziani, Bianca Maria; Zunino, Franco; Bianco, A. Raffaele; Ciardiello, Fortunato
CORPORATE SOURCE: Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli Federico II, Naples, 80131, Italy
SOURCE: Clinical Cancer Research (2001), 7(12), 4156-4163
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purpose: Protein kinase A type I (PKAI) and the epidermal growth factor receptor (EGFR) play a role in neoplastic transformation and interact with each other in transducing mitogenic signals. The authors developed different PKAI and EGFR inhibitors, demonstrating their cooperation with cytotoxic drugs and the therapeutic potential of the combined blockade of PKAI and EGFR. In this study, the authors investigated the effect of orally active PKAI and EGFR inhibitors in combination with a novel taxane. Exptl. Design: the authors combined a hybrid PKAI antisense oligonucleotide sequence (AS-PKAI), the EGFR inhibitor ZD1839 (Iressa), and the taxane IDN5109, studying their effect

on human cancer growth, apoptosis, and angiogenesis and measuring vascular endothelial growth factor (VEGF) expression and vessel formation in vitro and after oral administration in nude mice. Results: the authors demonstrated cooperative growth inhibitory and proapoptotic effects and inhibition of VEGF expression with any combination of two drugs and a marked synergistic effect when all three agents were combined. Oral administration of AS-PKAI, ZD1839, and IDN5109 in combination to nude mice caused a remarkable antitumor effect with no histol. evidence of tumors in 50% of mice 5 wk after treatment withdrawal, accompanied by complete suppression of vessel formation and VEGF expression. Conclusion: This is the first demonstration of the cooperative antitumor and antiangiogenic activity of three novel agents that block multiple signaling pathways after oral administration. Because all agents are under clin. evaluation in cancer patients, the authors' results provide a rationale to translate this feasible therapeutic strategy in a clin. setting.

IT 184475-35-2, ZD1839
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel taxane, antisense oligonucleotide targeting protein kinase A, and epidermal growth factor receptor inhibitor causes cooperative antitumor and antiangiogenic activity in human cancer cells and in mice)

RN 184475-35-2 CAPLUS

CN 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 35 THERE ARE 35 CAPLUS RECORDS THAT CITE THIS RECORD (35 CITINGS)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2001:921397 CAPLUS

DOCUMENT NUMBER: 137:87669

TITLE: Pharmacodynamic studies with the epidermal growth factor receptor tyrosine kinase inhibitor ZD1839

AUTHOR(S): Albanell, Joan; Rojo, Federico; Baselga, Jose

CORPORATE SOURCE: Medical Oncology Service, Vall d'Hebron Hospital, Barcelona, Spain

SOURCE: Seminars in Oncology (2001), 28(5, Suppl. 16), 56-66
CODEN: SOLGAV; ISSN: 0093-7754

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal; General Review

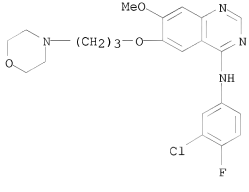
LANGUAGE: English

AB A review. ZD1839 is an orally active, selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells, and other host-dependent processes promoting cancer growth. Based on its promising preclin. antitumor activity and favorable toxicity profile, ZD1839 has recently entered clin. trials. A particular challenge in the clin. development of this exciting compound is to explore its biol. (pharmacodynamic) activity against the EGFR and receptor-dependent processes in serial biopsies. Such studies might be of assistance in predicting the subset of tumors that will benefit from therapy. They also may prove whether complete EGFR blockade is achieved in vivo. This latest point is particularly relevant because an optimal biol. dose (ie, a dose resulting in complete receptor inhibition) would be preferred to the maximally tolerated dose that is being used with conventional nontargeted chemotherapeutic drugs. A series of preclin. studies have identified potentially useful surrogate markers of EGFR activity (eg, phosphorylation of EGFR and downstream receptor-dependent mols. such as mitogen-activated protein kinase [MAPK], Akt, or p27) that could be used as a surrogate marker of ZD1839 efficacy. In various tumor types, such as head and neck squamous carcinoma and gastric and breast adenocarcinoma, a relation between EGFR and downstream markers (such as phosphorylated MAPK) has been characterized, further supporting the potential of these mols. for pharmacodynamic studies. Preliminary anal. of serial skin biopsies from patients participating in phase I trials has shown that ZD1839 results in substantial changes in EGFR-dependent mols., such as phosphorylated MAPK, p27, phosphorylated STAT3, and others. Based on these encouraging results, studies assessing activated EGFR, activated MAPK, and other selected markers in phase II trials in tumors from patients treated with ZD1839 are currently planned or ongoing.

IT 184475-35-2, ZD1839
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticancer studies with epidermal growth factor receptor tyrosine kinase inhibitor ZD1839)

RN 184475-35-2 CAPLUS

CN 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 36 THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (36 CITINGS)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 40 CAPLUS

ACCESSION NUMBER: 2001:839156 CAPLUS
DOCUMENT NUMBER: 136:144494
TITLE: Lung cancer
AUTHOR(S): Evans, Tracey L.; Lynch, Thomas J., Jr.
CORPORATE SOURCE: Massachusetts General Hospital Cancer Center, Boston, MA, 02114, USA
SOURCE: Oncologist (2001), 6(5), 407-414
CODEN: OCOLF6; ISSN: 1083-7159
PUBLISHER: AlphaMed Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Is any one combination therapy for metastatic non-small cell lung cancer (NSCLC) superior to other regimens for metastatic NSCLC. The answer is "probably number". More than 4000 patients with advanced NSCLC participated in randomized trials presented at the 37th Annual Meeting of the American Society of Clin. Oncol. TAX326 was the only study in which the investigational arm (cisplatin/docetaxel) showed a statistically significant difference in survival compared with the reference standard (cisplatin/vinorelbine). The authors did learn, however, that what is administered may make some difference: cisplatin might be superior to carboplatin, and patients treated with nonplatinum chemotherapy regimens have a trend toward poorer survival than those who receive platinum doublets. Although there is still no clear best regimen for advanced NSCLC, doctors may now know how much chemotherapy to give: a randomized study presented found that four cycles produces as much survival benefit as treating until progression. The most significant abstrs. presented at this year's lung cancer session involved the use of novel agents with unique mechanisms of action. The median survival in the large, randomized trials of chemotherapy in advanced NSCLC remains a bleak 9 mo. ISIS 3521, an antisense oligonucleotide that targets protein kinase C, was found to produce a near doubling of survival when combined with carboplatin and paclitaxel. OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, was shown to have impressive single agent activity in the second-line treatment of lung cancer. The future of lung cancer therapy will involve combining these novel agents with active chemotherapy regimens in an effort to improve outcome. While it appears that a plateau has been reached in what can be accomplished with various combinations of cytotoxic chemotherapy in metastatic NSCLC, in locally-advanced disease new chemotherapy combinations can achieve remarkable results when combined with radiation therapy. The Southwest Oncol. Group presented unprecedented phase II data on the use of cisplatin and etoposide with concurrent radiation therapy followed by consolidation docetaxel in patients with stage IIIB NSCLC.

IT 183319-69-9, OSI-774
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment options for humans with lung cancer)

RN 183319-69-9 CAPLUS

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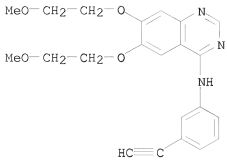

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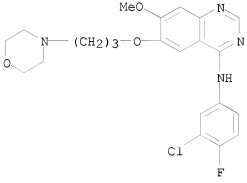
OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2001:817781 CAPLUS
DOCUMENT NUMBER: 136:128701
TITLE: ZD1839 (IRESSA), a novel epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, potently inhibits the growth of EGFR-positive cancer cell lines with or without erbB2 overexpression
AUTHOR(S): Anderson, Neil G.; Ahmad, Tawhid; Chan, Kai; Dobson, Richard; Bundred, Nigel J.
CORPORATE SOURCE: Division of Cancer Studies, Department of Surgery, School of Medicine, School of Biological Sciences, University of Manchester, Manchester, UK
SOURCE: International Journal of Cancer (2001), 94(6), 774-782 CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Overexpression of the growth factor receptors EGFR and erbB2 occurs frequently in several human cancers and is associated with aggressive tumor behavior and poor patient prognosis. We have investigated the effects of ZD1839 (Iressa), a novel EGFR tyrosine kinase inhibitor, on the growth, in vitro and in vivo, of human cancer cell lines expressing various levels of EGFR and erbB2. Proliferation of EGFR-overexpressing A431 and MDA-MB-231 cells in vitro was potently inhibited (50%-70%) by ZD1839 with half-maximally EDs in the low nanomolar range. In parallel, ZD1839 blocked autophosphorylation of EGFR and prevented activation of PLC-γI, ERK MAP kinases and PKB/Akt by EGF. It also inhibited proliferation in EGFR+ cancer cell lines overexpressing erbB2 (SKBr3, SKOV3, BT474) by between 20% and 80%, effects which correlated with inhibition of EGF-dependent erbB2 phosphorylation and activation of ERK MAP kinase and PKB/Akt in SKOV3 cells. Oral administration of ZD1839 inhibited the growth of MDA-MB-231 and SKOV3 tumors, established as xenografts in athymic mice, by 71% and 32%, resp. Growth inhibition coincided with reduced proliferation but no change in apoptotic index. Collectively, these results show that ZD1839, at the doses studied, is a potent inhibitor of proliferation not only in cells overexpressing EGFR but also in EGFR+ cells that overexpress erbB2.

IT 184475-35-2, ZD1839
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ZD1839 (IRESSA), a novel epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, potently inhibits the growth of EGFR-pos. cancer cell lines with or without erbB2 overexpression)
RN 184475-35-2 CAPLUS
CN 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 108 THERE ARE 108 CAPLUS RECORDS THAT CITE THIS RECORD (108 CITINGS)
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

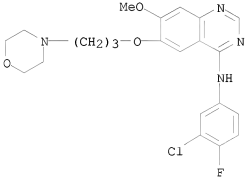
L5 ANSWER 23 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2001:473614 CAPLUS
DOCUMENT NUMBER: 135:205681
TITLE: Enhanced epidermal growth factor receptor signaling in MCF7 breast cancer cells after long-term culture in the presence of the pure antiestrogen ICI 182,780 (Faslodex)
AUTHOR(S): McClelland, Richard A.; Barrow, Denise; Madden, Tracie-Ann; Dutkowski, Carol M.; Pamment, Joanna; Knowlden, Janice M.; Gee, Julia M. W.; Nicholson, Robert I.
CORPORATE SOURCE: Tenovus Cancer Research Center, Welsh School of Pharmacy, Cardiff University, Cardiff, CF10 3XF, UK
SOURCE: Endocrinology (2001), 142(7), 2776-2788
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This paper describes the establishment of an antiestrogen-resistant MCF7 breast cancer cell subline (FASMCF) by continuous culture of the estrogen-responsive parental line in steroid-depleted, ICI 182,780 (Faslodex; 10-7 M)-supplemented medium. After a 3-mo period of growth suppression, cells began to proliferate in ICI 182,780 at rates similar to those of untreated wild-type cells. Immunocytochem. showed these cells to have reduced estrogen receptor and an absence of progesterone receptor proteins. RT-PCR and transient transfection studies with estrogen response element-reporter constructs confirmed that ICI 182,780-suppressed estrogen response element-mediated signaling. FASMCF cells show increased dependence upon epidermal growth factor receptor (EgfR)/mitogen-activated

protein kinase (MAPK)-mediated signaling. Thus, EgfR protein and mRNA, growth responses to transforming growth factor-α, and extracellular signal-regulated kinase 1/2 MAPK activation levels are all increased. Unlike wild-type cells, FASMCF cells are highly sensitive to growth inhibition by an EgfR-specific tyrosine-kinase inhibitor (TKI), ZD1839 (Iressa), and an inhibitor of the activation of MEK1 (MAPKK), PD098059. Short-term (.apprx.3 wk) withdrawal of cells from antiestrogen had no effect on growth or phenotype, whereas longer withdrawal (>10 wk) appeared to partially reverse the cellular phenotype with increasing estrogen receptor and decreasing EgfR levels. In subsequent studies FASMCF cells were maintained in TKI, where their growth was again suppressed and secondary TKI resistance failed to develop within the 3-mo period in which initial ICI 182,780 resistance arose. Furthermore, wild-type cells similarly maintained in combination ICI 182,780 and TKI treatment conditions remained growth arrested (>6 mo), with notable cell loss through both reduced rates of cellular proliferation and increased cell death.

IT 184475-35-2, Iressa
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ZD 1839; enhanced EGF receptor signaling in MCF7 breast cancer cells after long-term culture in presence of pure antiestrogen ICI 182780 (Faslodex))

RN 184475-35-2 CAPLUS

CN 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 136 THERE ARE 136 CAPLUS RECORDS THAT CITE THIS RECORD (136 CITINGS)

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 24 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2001:372383 CAPLUS

DOCUMENT NUMBER: 135:118641

TITLE: Structural Determinants for Potent, Selective Dual Site Inhibition of Human pp60c-src by 4-Anilinoquinazolines

AUTHOR(S): Tian, Gaochao; Cory, Michael; Smith, Albert A.; Knight, W. Blaine

CORPORATE SOURCE: Departments of Molecular Biochemistry and Structural Chemistry, GlaxoSmithKline Research and Development, Research Triangle Park, NC, 27709, USA

SOURCE: Biochemistry (2001), 40(24), 7084-7091
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The kinetic mechanisms for the inhibition of pp60c-src tyrosine kinase (Src TK) by 4-anilinoquinazolines, an important class of chems. as protein kinase inhibitors, were investigated. 4-Anilinoquinazolines with a bulky group at the 4'-position of the anilino group were shown to be competitive with both ATP and peptide, whereas mols. lacking such a bulky group only displayed an inhibition pattern typical of those competitive with ATP and noncompetitive with peptide. Modifications of the substituents on the carbocyclic ring did not perturb the inhibition pattern although the affinities of these modified inhibitors for Src TK were affected. Structural modeling of Src TK with inhibitor and peptide substrate bound indicated a direct atomic conflict between the bulky 4-position group and the hydroxy of the peptide tyrosyl to which the γ-phosphate of ATP is transferred during the kinase reaction. This atomic conflict would likely prevent simultaneous binding of both inhibitor and peptide, consistent with the observed kinetic competitiveness of the inhibitor with peptide. The dual site inhibitors appeared to have both enhanced potency and selectivity for Src TK. One such inhibitor, 4-(4'-phenoxyanilino)-6,7-dimethoxyquinazoline, had a 15 nM potency against Src TK and was selective over receptor tyrosine kinases VEGFR2 by 88-fold and C-fms by 190-fold.

IT 153437-79-7 159768-23-7 179247-15-5
179248-59-0 179248-61-4 179248-68-1
202475-38-5 211555-08-7 309739-66-0
351377-16-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(structural determinants for potent, selective dual site inhibition of human pp60c-src protein tyrosine kinase by 4-anilinoquinazolines)

RN 153437-79-7 CAPLUS
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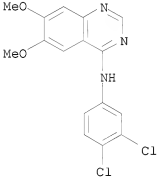

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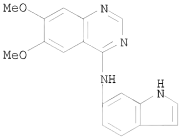

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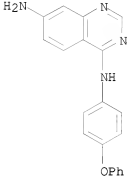

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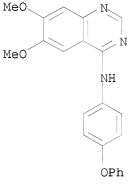

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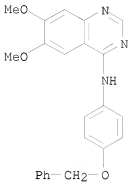

RN 179248-68-1 CAPLUS
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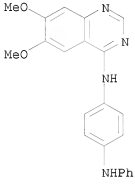

RN 202475-38-5 CAPLUS
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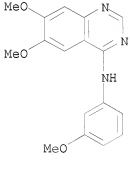

RN 211555-08-7 CAPLUS
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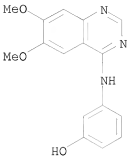

RN 309739-66-0 CAPLUS
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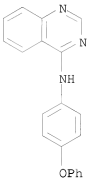
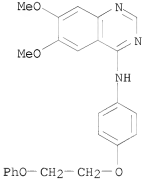


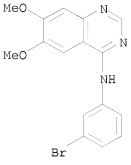
RN 351377-16-7 CAPLUS
CN 4-Quinazolinamine, 6,7-dimethoxy-N-[4-(2-phenoxyethoxy)phenyl]- (CA INDEX NAME)



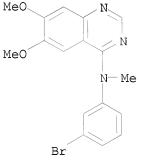
OS.CITING REF COUNT: 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 25 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2001:187878 CAPLUS

DOCUMENT NUMBER: 134:361107
TITLE: DNA Interaction of the Tyrosine Protein Kinase Inhibitor PD153035 and Its N-Methyl Analogue
AUTHOR(S): Goossens, Jean-Francois; Bouey-Bencteux, Edith; Houssin, Raymond; Henichart, Jean-Pierre; Colson, Pierre; Houssier, Claude; Laine, William; Baldeyrou, Brigitte; Bailly, Christian
CORPORATE SOURCE: Laboratoire de Chimie Analytique Faculte des Sciences Pharmaceutiques et Biologiques and Institut de Chimie Pharmaceutique Albert Lespagnol (EA2692), Universite de Lille, Lille, 59006, Fr.
SOURCE: Biochemistry (2001), 40(15), 4663-4671
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The brominated anilinoquinazoline derivative PD153035 exhibits a very high affinity and selectivity for the epidermal growth factor receptor tyrosine kinase (EGF-R TK) and shows a remarkable cytotoxicity against several types of tumor cell lines. In contrast, its N-Me derivative, designated EBE-A22, has no effect on EGF-R TK but maintains a high cytotoxic profile. The present study was performed to explore the possibility that PD153035 and its N-Me analog might interact with double-stranded DNA, which is a primary target for many conventional antitumor agents. We studied the strength and mode of binding to DNA of PD153035 and EBE-A22 by means of absorption, fluorescence, and circular and linear dichroism as well as by a relaxation assay using human DNA topoisomerases. The results of various optical and gel electrophoresis techniques converge to show that both drugs bind to DNA and behave as typical intercalating agents. In particular, EBE-A22 unwinds supercoiled plasmid, stabilizes duplex DNA against heat denaturation, and produces neg. CD and ELD signals, as expected for an intercalating agent. Extensive DNase I footprinting expts. performed with a large range of DNA substrates show that EBE-A22, but not PD153035, interacts preferentially with GC-rich sequences and discriminates against homo-oligomeric runs of A and T which are often cut more readily by the enzyme in the presence of the drug compared to the control. Altogether, the results provide the first exptl. evidence that DNA is a target of anilinoquinazoline derivs. and suggest that this N-methylated ring system is a valid candidate for the development of DNA-targeted cytotoxic compds. The possible relevance of selective DNA binding to activity is considered. The unexpected GC-selective binding properties of EBE-A22 entreat further exploration into the use of N-methylanilinoquinazoline derivs. as tools for designing sequence-specific DNA binding ligands.
IT 153436-54-5, PD153035 229476-53-3, EBE-A 22
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DNA interaction of tyrosine protein kinase inhibitor PD153035 and N-Me analog)
RN 153436-54-5 CAPLUS
CN 4-Quinazolinamine, N-(3-bromophenyl)-6,7-dimethoxy- (CA INDEX NAME)



RN 229476-53-3 CAPLUS
CN 4-Quinazolinamine, N-(3-bromophenyl)-6,7-dimethoxy-N-methyl- (CA INDEX NAME)



OS.CITING REF COUNT: 20 THERE ARE 20 CAPLUS RECORDS THAT CITE THIS RECORD (20 CITINGS)
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

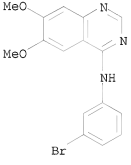
L5 ANSWER 26 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2000:718482 CAPLUS
DOCUMENT NUMBER: 134:50976
TITLE: Classification of Kinase Inhibitors Using BCUT Descriptors
AUTHOR(S): Pirard, Bernard; Pickett, Stephen D.
CORPORATE SOURCE: Aventis Pharma, Dagenham Research Centre, Dagenham Essex, RM10 7XS, UK
SOURCE: Journal of Chemical Information and Computer Sciences (2000), 40(6), 1431-1440
CODEN: JCISD8; ISSN: 0095-2338
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB BCUTs are an interesting class of mol. descriptor which have been proposed for a number of design and QSAR type tasks. It is important to understand what kind of information any particular descriptor encodes and to be able to relate this to the biol. properties of the mols. In this paper the authors present studies with BCUTs for the classification of ATP site directed kinase inhibitors active against five different protein kinases: three from the serine/threonine family and two from the tyrosine kinase family. In combination with a chemometric method, PLS discriminant anal., the BCUTs are able to correctly classify the ligands according to their

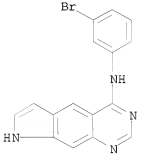
target. A novel class of kinase inhibitors is correctly predicted as inhibitors of the EGFR tyrosine kinase. Comparison with other descriptor types such as two-dimensional fingerprints and three-dimensional pharmacophore-based descriptors allows the authors to gain an insight into the level of information contained within the BCUTs.

IT 153436-54-5, PD153035 171179-29-6
256521-38-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(classification of protein kinase inhibitors directed towards ATP site using BCUT descriptors)

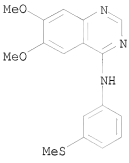
RN 153436-54-5 CAPLUS
CN 4-Quinazolinamine, N-(3-bromophenyl)-6,7-dimethoxy- (CA INDEX NAME)



RN 171179-29-6 CAPLUS
CN 8H-Pyrrolo[3,2-g]quinazolin-4-amine, N-(3-bromophenyl)- (CA INDEX NAME)



RN 256521-38-7 CAPLUS
CN 4-Quinazolinamine, 6,7-dimethoxy-N-[3-(methylthio)phenyl]- (CA INDEX NAME)

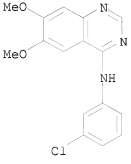


OS.CITING REF COUNT: 46 THERE ARE 46 CAPLUS RECORDS THAT CITE THIS RECORD (46 CITINGS)
REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 27 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2000:702602 CAPLUS
DOCUMENT NUMBER: 134:3338
TITLE: Transactivation of the epidermal growth factor receptor in endothelin-1-induced mitogenic signaling in human ovarian carcinoma cells
AUTHOR(S): Vacca, Fabrizio; Bagnato, Anna; Catt, Kevin J.; Tecce, Raffaele
CORPORATE SOURCE: Laboratory of Molecular Pathology and Ultrastructure, Regina Elena Cancer Institute, Rome, 00158, Italy
SOURCE: Cancer Research (2000), 60(18), 5310-5317
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

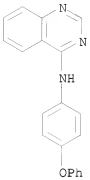
AB Endothelin (ET)-1 is produced in ovarian carcinoma cells and is known to act through ETA receptors as an autocrine growth factor in vitro and in vivo. In OVCA 433 human ovarian carcinoma cells, ET-1 caused phosphorylation of the epidermal growth factor receptor (EGF-R) that was accompanied by phosphorylation of Shc and its recruitment complexed with Grb2. These findings suggested that an EGF-R/ras-dependent pathway may contribute to the activation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) 2 and mitogenic signaling induced by ET-1 in these cells. Specific inhibition of EGF-R kinase activity by tyrphostin AG1478 prevented ET-1-induced transactivation of the EGF-R, as well as Shc phosphorylation and recruitment with Grb2. Furthermore, ET-1-induced activation of Erk 2 was partially inhibited by tyrphostin AG1478. In accord with this finding, the mitogenic action of ET-1 in OVCA 433 cells was also significantly reduced by a concentration of tyrphostin AG1478 that abolished the growth response of EGF-stimulated cells. Inhibition of protein kinase C activity, which contributes to the proliferative action of ET-1 in OVCA 433 cells, had no effect on the activation of Erk 2 by ET-1, which suggests that this effect of protein kinase C does not involve ras-independent activation of Erk 2. Inhibition by wortmannin of PI3-kinase activity, which has been implicated in ET-1 and other G protein-coupled receptor (GPCR)-mediated signaling pathways, reduced Erk 2 activation by ET-1 but had no effect on ET-1-induced EGF-R and Shc phosphorylation. These findings indicate that ET-1-induced stimulation of Erk 2 phosphorylation, and mitogenic responses in OVCA 433 ovarian cancer cells are mediated in part by signaling pathways that are

initiated by transactivation of the EGF-R.
IT 153436-53-4, Tyrphostin AG 1478
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(effect on transactivation of the EGFR in endothelin-1-induced mitogenic signaling in human ovarian carcinoma cells)
RN 153436-53-4 CAPLUS
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 82 THERE ARE 82 CAPLUS RECORDS THAT CITE THIS RECORD (82 CITINGS)
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 28 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2000:656736 CAPLUS
DOCUMENT NUMBER: 134:13075
TITLE: Pyrrolo[2,3-d]pyrimidines containing an extended 5-substituent as potent and selective inhibitors of lck I
AUTHOR(S): Arnold, L. D.; Calderwood, D. J.; Dixon, R. W.; Johnston, D. N.; Kamens, J. S.; Munschauer, R.; Rafferty, P.; Ratnofsky, S. E.
CORPORATE SOURCE: BASF Bioresearch Corporation, Worcester, MA, 01605-5314, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(19), 2167-2170
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pyrrolo[2,3-d]pyrimidines containing a 5-(4-phenoxyphenyl) substituent are potent and selective inhibitors of lck in vitro; some compds. are selective for lck over src. Data are shown for two compds. demonstrating that they are potent and selective inhibitors of IL2 production in cells.
IT 309739-66-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(pyrrolopyrimidines as potent and selective inhibitors of lck I)
RN 309739-66-0 CAPLUS
CN 4-Quinazolinamine, N-(4-phenoxyphenyl)- (CA INDEX NAME)



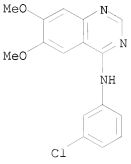
OS.CITING REF COUNT: 57 THERE ARE 57 CAPLUS RECORDS THAT CITE THIS RECORD (57 CITINGS)
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 29 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2000:603443 CAPLUS
DOCUMENT NUMBER: 133:261188
TITLE: Blockade of the epidermal growth factor receptor tyrosine kinase suppresses tumorigenesis in MMTV/Neu + MMTV/TGF-α bigenic mice
AUTHOR(S): Lenferink, Anne E. G.; Simpson, Jean F.; Shawver, Laura K.; Coffey, Robert J.; Forbes, James T.; Arteaga, Carlos L.
CORPORATE SOURCE: Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, 37232, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(17), 9609-9614
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Overexpression of ErbB-2/Neu has been causally associated with mammary epithelial transformation. Here we report that blockade of the epidermal growth factor receptor (EGFR) kinase with AG-1478 markedly delays breast tumor formation in mouse mammary tumor virus (MMTV)/Neu + MMTV/transforming growth factor α bigenic mice. This delay was associated with inhibition of EGFR and Neu signaling, reduction of cyclin-dependent kinase 2 (Cdk2) and mitogen-activated protein kinase (MAPK) activities and cyclin D1, and an increase in the levels of the Cdk inhibitor p27Kip1. In addition, BrdUrd incorporation into tumor cell nuclei was prevented with no signs of tumor cell apoptosis. These observations prompted us to investigate the stability of p27. Recombinant p27 was degraded rapidly in vitro by untreated but not by AG-1478-treated tumor lysates. Proteasome depletion of the tumor lysates, addition of the specific MEK1/2 inhibitor U-0126, or a T187A mutation in recombinant p27 all prevented p27 degradation Cdk2 and MAPK ppts. from untreated tumor lysates phosphorylated recombinant wild-type p27 but not the T187A mutant in vitro. Cdk2 and MAPK ppts. from AG-1478-treated tumors were unable to phosphorylate p27 in vitro. These data suggest that increased signaling by ErbB receptors up-regulates MAPK activity, which, in turn, phosphorylates and destabilizes p27, thus contributing to dysregulated cell cycle progression.

IT 153436-53-4, AG-1478

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(blockade of the epidermal growth factor receptor tyrosine kinase suppresses tumorigenesis in MMTV/Neu + MMTV/TGF-α bigenic mice)
RN 153436-53-4 CAPLUS
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 87 THERE ARE 87 CAPLUS RECORDS THAT CITE THIS RECORD (87 CITINGS)
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

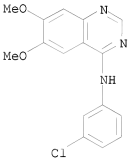
L5 ANSWER 30 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2000:259048 CAPLUS
DOCUMENT NUMBER: 133:27497
TITLE: Peroxynitrite Modulates the Activation of p38 and Extracellular Regulated Kinases in PC12 Cells
AUTHOR(S): Jope, Richard S.; Zhang, Liang; Song, Ling
CORPORATE SOURCE: Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, AL, 35294-0017, USA
SOURCE: Archives of Biochemistry and Biophysics (2000), 376(2), 365-370
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although peroxynitrite appears to contribute to neuronal dysfunction in several neurodegenerative disorders, little is known about how peroxynitrite affects cellular signaling processes. This study investigated if peroxynitrite affects the mitogen-activated protein kinases, extracellular-regulated kinases 1 and 2 (ERK1/2) and p38. Exposure of PC12 cells to 500 μM peroxynitrite activated ERK1/2 and p38 within 5 min and this was followed by gradual decreases in activation over the next 25 min. Activation of ERK1/2 by peroxynitrite was mediated by activation of the epidermal growth factor (EGF) receptor in a calcium/calmodulin-dependent kinase II- and src family tyrosine kinase-dependent manner, as it was blocked by the selective EGF receptor inhibitor AG1478, by KN62, an inhibitor of calcium/calmodulin-dependent kinase II, and by PP1, a src family tyrosine kinase inhibitor. Activation of p38 by peroxynitrite was independent of the EGF receptor, required activation of calcium/calmodulin-dependent kinase II and src family tyrosine kinases, and was modulated by nerve growth factor (NGF) in a time-dependent manner. Pretreatment with NGF (2 h) attenuated, whereas cotreatment with NGF potentiated, peroxynitrite-induced activation of p38.

Thus, peroxynitrite activates ERK1/2 and p38, activation of EGF receptors, calcium/calmodulin-dependent kinase II, and src family tyrosine kinases participate in these signaling responses to peroxynitrite, and peroxynitrite- and NGF-induced signaling activities converge on p38. (c) 2000 Academic Press.

IT 153436-53-4, AG1478
RL: ARG (Analytical reagent use); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(EGF receptor inhibitor; peroxynitrite modulates the activation of p38 and extracellular regulated kinases in PC12 cells)

RN 153436-53-4 CAPLUS

CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 61 THERE ARE 61 CAPLUS RECORDS THAT CITE THIS RECORD (61 CITINGS)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 31 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2000:12514 CAPLUS

DOCUMENT NUMBER: 133:271

TITLE: Influence of protein kinase inhibitors on Streptococcus uberis internalization into bovine mammary epithelial cells

AUTHOR(S): Almeida, Raul A.; Calvinho, Luis F.; Oliver, Stephen P.

CORPORATE SOURCE: Department of Animal Science, Institute of Agriculture, University of Tennessee, Knoxville, TN, 37996, USA

SOURCE: Microbial Pathogenesis (2000), 28(1), 9-16
CODEN: MIPAEV; ISSN: 0882-4010

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

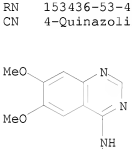
AB Previous reports indicated that bovine mammary epithelial cells internalized Streptococcus uberis, a bovine mastitis pathogen, and that inhibitors of F-actin microfilament polymerization inhibited bacterial internalization into mammary epithelial cells. In the present report, we show that inhibitors of eukaryotic cell tyrosine protein kinase (TPK) and protein kinase C (PKC), staurosporine, genistein and tyrphostin, significantly reduced internalization of S. uberis into mammary epithelial cells. Short-term treatment (15 min) of mammary epithelial cells with 12- O -tetradecanoylphorbol-13-acetate (TPA), shown previously to up-regulate

activity of PKC, significantly increased internalization of S. uberis. Conversely, long-term incubation (24 h) of epithelial cells with TPA, which down-regulates PKC activity, significantly reduced the number of internalized S. uberis. These results suggest that protein kinases (TPK and PKC) are involved in internalization of S. uberis into bovine mammary epithelial cells. Identification of host cell surface receptor(s) and ligands that trigger the uptake signal by S. uberis need to be delineated. (c) 2000 Academic Press.

IT 153436-53-4, AG 1478
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protein kinase inhibitors effect on Streptococcus uberis internalization into bovine mammary epithelial cells)

RN 153436-53-4 CAPLUS

CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 32 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 1999:777762 CAPLUS

DOCUMENT NUMBER: 132:132307

TITLE: Binding mode of the 4-anilinoquinazoline class of protein kinase inhibitor: X-ray crystallographic studies of 4-anilinoquinazolines bound to cyclin-dependent kinase 2 and p38 kinase

AUTHOR(S): Shewchuk, Lisa; Hassell, Anne; Wisely, Bruce; Rocque, Warren; Holmes, William; Veal, James; Kuyper, Lee F.

CORPORATE SOURCE: Glaxo Wellcome Inc., Research Triangle Park, NC, 27709, USA

SOURCE: Journal of Medicinal Chemistry (2000), 43(1), 133-138 CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

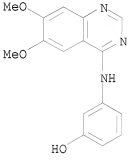
LANGUAGE: English

AB 4-Anilinoquinazolines represent an important class of protein kinase inhibitor. Modes of binding for two members of this inhibitor class were determined by x-ray crystallog. anal. of one inhibitor (4-[3-hydroxyanilino]-6,7-dimethoxyquinazoline) in complex with cyclin-dependent kinase 2 (CDK2) and the other (4-[3-methylsulfanylanilino]-6,7-dimethoxyquinazoline) in complex with p38 kinase. In both inhibitor/kinase structures, the 4-anilinoquinazoline was bound in the ATP site with the quinazoline ring system oriented along the

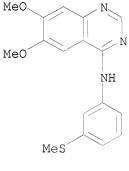
peptide strand that links the two domains of the protein and with the anilino substituent projecting into a hydrophobic pocket within the protein interior. In each case, the nitrogen at position-1 of the quinazoline accepted a hydrogen bond from a backbone NH (CDK2, Leu-83; p38, Met-109) of the domain connector strand, and aromatic hydrogen atoms at C2 and C8 interacted with backbone carbonyl oxygen atoms of the peptide strand. The anilino group of the CDK2-bound compound was essentially coplanar with the quinazoline ring system and occupied a pocket between Lys-33 and Phe-80. For the p38-bound inhibitor, the anilino group was angled out of plane and was positioned between Lys-53 and Thr-106 in a manner similar to that observed for the aryl substituent of the pyridinylimidazole class of inhibitor.

IT 211555-08-7 256521-38-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(x-ray crystallog. of 4-anilinoquinazoline class of protein kinase inhibitor binding to cyclin-dependent kinase 2 and p38 kinase)

RN 211555-08-7 CAPLUS
CN Phenol, 3-[(6,7-dimethoxy-4-quinazolinyl)amino]- (CA INDEX NAME)



RN 256521-38-7 CAPLUS
CN 4-Quinazolinamine, 6,7-dimethoxy-N-[3-(methylthio)phenyl]- (CA INDEX NAME)



OS.CITING REF COUNT: 129 THERE ARE 129 CAPLUS RECORDS THAT CITE THIS RECORD (131 CITINGS)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

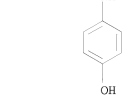
L5 ANSWER 33 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1999:622744 CAPLUS

DOCUMENT NUMBER: 131:309757
TITLE: Targeting Janus kinase 3 in mast cells prevents immediate hypersensitivity reactions and anaphylaxis
AUTHOR(S): Malaviya, Ravi; Zhu, DeMin; Dibirdik, Ilker; Uckun, Fatih M.
CORPORATE SOURCE: Department of Allergy, Hughes Institute, St. Paul, MN, 55113, USA
SOURCE: Journal of Biological Chemistry (1999), 274(38), 27028-27038
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Janus kinase 3 (JAK3), a member of the Janus family protein-tyrosine kinases, is expressed in mast cells, and its enzymic activity is enhanced by IgE receptor/FcεRI crosslinking. Selective inhibition of JAK3 in mast cells with 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131) blocked the phospholipase C activation, calcium mobilization, and activation of microtubule-associated protein kinase after IgE receptor/FcεRI crosslinking. Treatment of IgE-sensitized rodent as well as human mast cells with WHI-P131 effectively inhibited the activation-associated morphol. changes, degranulation, and proinflammatory mediator release after specific antigen challenge without affecting the functional integrity of the distal secretory machinery. In vivo administration of the JAK3 inhibitor WHI-P131 prevented mast cell degranulation and development of cutaneous as well as systemic fatal anaphylaxis in mice at nontoxic dose levels. Thus, JAK3 plays a pivotal role in IgE receptor/FcεRI-mediated mast cell responses, and targeting JAK3 with a specific inhibitor, such as WHI-P131, may provide the basis for new and effective treatment as well as prevention programs for mast cell-mediated allergic reactions.

IT 202475-60-3, WHI-P131
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting JAK3 in mast cells prevents immediate hypersensitivity reactions and anaphylaxis)

RN 202475-60-3 CAPLUS
CN Phenol, 4-[(6,7-dimethoxy-4-quinazolinyl)amino]- (CA INDEX NAME)



OS.CITING REF COUNT: 46 THERE ARE 46 CAPLUS RECORDS THAT CITE THIS RECORD (47 CITINGS)
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS

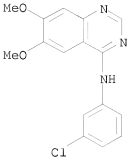
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 34 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1999:443061 CAPLUS
DOCUMENT NUMBER: 131:226472
TITLE: Regulation of Na+-K+-2Cl- cotransport by protein phosphorylation in ferret erythrocytes
AUTHOR(S): Flatman, Peter W.; Creanor, James
CORPORATE SOURCE: Membrane Biology Group, Department of Biomedical Sciences, University Medical School, Edinburgh, EH8 9AG, UK
SOURCE: Journal of Physiology (Cambridge, United Kingdom) (1999), 517(3), 699-708
CODEN: JPHYA7; ISSN: 0022-3751
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Na+-K+-2Cl- cotransport in ferret erythrocytes was measured as the bumetanide-sensitive uptake of 86Rb. The resting cotransport rate was high but could be increased threefold by treating erythrocytes with calyculin A, a potent inhibitor of serine/threonine phosphatases. Twenty nanomolar was sufficient to maximally and rapidly (within 4 min) stimulate transport. The effects of several kinase inhibitors were tested. High concns. of K-252a, K-252b, calphostin C and hypericin caused less than 20% inhibition. Staurosporine (IC50, 0.06 μM) and 4-amino-5-(4-methylphenyl)-7-(t-butyl)pyrazolo[3,4-d]pyrimidine (PP1; IC50, 2.5 μM) were more potent but still only partially (40-50%) inhibited transport, an effect mimicked by reducing ionized intracellular Mg2+ concentration to submicromolar levels. Genistein may inhibit all transport at a sufficiently high dose (IC50, 0.36 mM) perhaps by directly inhibiting the transporter. Staurosporine, PP1 and the removal of Mg2+ all prevented subsequent stimulation by calyculin A, and all inhibited calyculin-stimulated transport by 20-30%. The effects of staurosporine, PP1 and Mg2+ removal were not additive. The phosphatase that dephosphorylates the cotransporter is probably Mg2+ (or possibly Ca2+ or Mn2+) sensitive and not the target for calyculin A. The data suggest that this phosphatase is inhibited by phosphorylation, and that it is the regulation of this process which is affected by calyculin A and the kinase inhibitors tested here. Phosphorylation of the phosphatase is probably regulated by members of the Src family of tyrosine kinases.

IT 153436-53-4, AG1478
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of inhibitors of kinases and phosphatases on Na+-K+-2Cl- cotransport in ferret erythrocytes)

RN 153436-53-4 CAPLUS
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

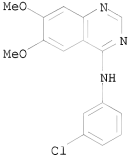
L5 ANSWER 35 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1998:319418 CAPLUS
DOCUMENT NUMBER: 129:62930
ORIGINAL REFERENCE NO.: 129:12905a,12908a
TITLE: Inhibition of platelet-derived growth factor and epidermal growth factor receptor signaling events after treatment of cells with specific synthetic inhibitors of tyrosine kinase phosphorylation
AUTHOR(S): Lipson, Kenneth E.; Pang, Long; Huber, L. Julie; Chen, Hui; Tsai, Jian-Ming; Hirth, Peter; Gazit, Aviv; Levitzki, Alexander; Mcmahon, Gerald
CORPORATE SOURCE: SUGEN, Inc., Redwood City, CA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1998), 285(2), 844-852
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The receptor kinase activity associated with the epidermal growth factor (EGF) receptor and platelet-derived growth factor (PDGF) receptor plays an important role in ligand-induced signaling events. The effect of specific, synthetic chemical inhibitors of PDGF- and EGF-mediated receptor tyrosine autophosphorylation on receptor signaling were examined in NIH 3T3 cells overexpressing PDGF of EGF receptors. Specific inhibition of ligand-dependent receptor autophosphorylation, PI3K activation, mitogen-activated protein kinase (MAPK) activation, cyclin E-associated kinase activity and cell proliferation was measured after treatment of cells with these inhibitors. A synthetic PDGF receptor kinase inhibitor exhibited specific inhibitory properties when tested for PDGF-induced receptor autophosphorylation, MAPK activity, PI3K activation, entry into S phase and cyclin E-associated kinase activity. A synthetic EGF receptor kinase inhibitor showed selective inhibitory properties when tested for EGF-induced receptor autophosphorylation, MAPK activation, PI3K activation, entry into S phase and cyclin E-associated kinase activity. In both cases, these compds. were found to be effective as inducers of growth arrest and accumulation of cells in the G1 phase of the cell cycle after ligand treatment. However, at high concns., the EGF receptor kinase inhibitor was observed to exhibit some non-specific effects as demonstrated by attenuation of PDGF-induced receptor autophosphorylation and cell cycle progression. This demonstrates that it is critical to use the lowest concentration

of such an inhibitor that will alter the response under investigation, to have confidence that the conclusions derived from the use of such inhibitor are valid. We conclude that these exptl. parameters signify useful end points to measure the relative selectivity of tyrosine kinase inhibitors that affect receptor-mediated signal transduction.

IT 153436-53-4, AG1478
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibition of platelet-derived growth factor and epidermal growth factor receptor signaling events after treatment of cells with specific synthetic inhibitors of tyrosine kinase phosphorylation)

RN 153436-53-4 CAPLUS
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 34 THERE ARE 34 CAPLUS RECORDS THAT CITE THIS RECORD (34 CITINGS)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

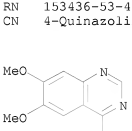
L5 ANSWER 36 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1997:593456 CAPLUS
DOCUMENT NUMBER: 127:272367
ORIGINAL REFERENCE NO.: 127:53009a,53012a
TITLE: Inhibitors of epidermal growth factor receptor kinase and of cyclin-dependent kinase 2 activation induce growth arrest, differentiation, and apoptosis of human papilloma virus 16-immortalized human keratinocytes
AUTHOR(S): Ben-Bassat, Hannah; Rosenbaum-Mitrani, Stella; Hartzstark, Zippora; Shlomai, Zippora; Kleinberger-Doron, Nurit; Gazit, Aviv; Plowman, Gregory; Levitzki, Rubina; Tsvieli, Rimona; Levitzki, Alexander
CORPORATE SOURCE: Laboratory of Experimental Surgery, Hadassah University Hospital, Jerusalem, IL-Q1120, Israel
SOURCE: Cancer Research (1997), 57(17), 3741-3750
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human papilloma virus 16 (HPV 16) is associated with cervical cancer and is therefore considered a major health risk for women. Immortalization of keratinocytes induced by HPV infection is largely due to the binding of p53 and Rb by the viral oncoproteins E6 and E7, resp., and is driven to a large extent by a transforming growth factor α/amphiregulin epidermal growth factor receptor autocrine loop. In this study, we show that the growth of HPV 16-immortalized human

keratinocytes can be blocked by a selective epidermal growth factor receptor kinase inhibitor, AG 1478, and by AG 555, a blocker of cyclin-dependent kinase 2 (Cdk2) activation. AG 1478 induces a massive increase in the Cdk2 protein inhibitors p27 and p21, whereas AG 555 appears to have a different mechanism of action, inhibiting the activation of Cdk2. Growth arrest induced by AG 1478 and AG 555 is accompanied by up to 20% of cells undergoing apoptosis. Following AG 1478 treatment but not AG 555 treatment, up to 50% of cells undergo terminal keratinocyte differentiation as determined by filaggrin expression and by the decline in the expression of cytokeratin 14. The growth-arresting properties of AG 1478 and AG 555 identifies them as possible lead antipapilloma agents.

IT 153436-53-4, AG 1478
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanism of antipapilloma activity of AG 1478 and AG 555)

RN 153436-53-4 CAPLUS
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 43 THERE ARE 43 CAPLUS RECORDS THAT CITE THIS RECORD (43 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

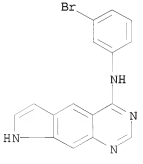
L5 ANSWER 37 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1997:262273 CAPLUS
DOCUMENT NUMBER: 126:277441
ORIGINAL REFERENCE NO.: 126:53787a,53790a
TITLE: Tyrosine Kinase Inhibitors. 11. Soluble Analogs of Pyrrolo- and Pyrazoloquinazolines as Epidermal Growth Factor Receptor Inhibitors: Synthesis, Biological Evaluation, and Modeling of the Mode of Binding
AUTHOR(S): Palmer, Brian D.; Trumpp-Kallmeyer, Susanne; Fry, David W.; Nelson, James M.; Showalter, H. D. Hollis; Denny, William A.
CORPORATE SOURCE: Cancer Society Research Laboratory Faculty of Medicine and Health Science, University of Auckland School of Medicine, Auckland, 1000, N. Z.
SOURCE: Journal of Medicinal Chemistry (1997), 40(10), 1519-1529
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new route to N-1-substituted pyrazolo- and pyrroloquinazolines has been developed from known quinazolones, via conversion to the corresponding

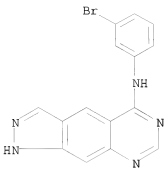
thiones, S-methylation to the thioethers, N-1-alkylation, and coupling with 3-bromoaniline. C-3-Substituted pyrroloquinazolines were prepared by Mannich base chemical A series of compds. bearing solubilizing side chains at these positions has been prepared and evaluated for inhibition of the tyrosine kinase activity of the isolated epidermal growth factor receptor (EGFR) and of its autophosphorylation in EGF-stimulated A431 cells. Several analogs, particularly C-3-substituted pyrroloquinazolines, retained high potency in both assays. A model for the binding of the general class of 4-anilinoquinazolines to the EGFR was constructed from structural information (particularly for the catalytic subunit of the cAMP-dependent protein kinase) and structure-activity relationships (SAR) in the series. In this model, the pyrrole ring in pyrroloquinazolines (and the 6- and 7-positions of quinazoline and related pyridopyrimidine inhibitors) occupies the entrance of the ATP binding pocket of the enzyme, with the pyrrole nitrogen located at the bottom of the cleft and the pyrrole C-3 position pointing toward a pocket corresponding to the ribose binding site of ATP. This allows considerable bulk tolerance for C-3 substituents and lesser but still significant bulk tolerance for N-1 substituents. The observed high selectivity of these compds. for binding to EGFR over other similar tyrosine kinases is attributed to the 4-anilino ring binding in an adjacent hydrophobic pocket which has an amino acid composition unique to the EGFR. The SAR seen for inhibition of the isolated enzyme by the pyrazolo- and pyrroloquinazolines discussed here is fully consistent with this binding model. For the N-1-substituted compds., inhibition of autophosphorylation in A431 cells correlates well with inhibition of the isolated enzyme, as seen previously for related pyridopyrimidines. However, the C-3-substituted pyrroloquinazolines show unexpectedly high potencies in the autophosphorylation assay, making them of particular interest.

IT 171179-29-6 174709-35-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(preparation of pyrrolo- and pyrazoloquinazolines as epidermal growth factor receptor inhibitors)

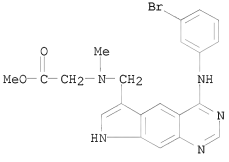
RN 171179-29-6 CAPLUS
CN 8H-Pyrrolo[3,2-g]quinazolin-4-amine, N-(3-bromophenyl)- (CA INDEX NAME)



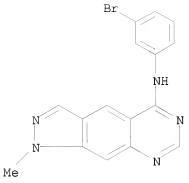
RN 174709-35-4 CAPLUS
CN 1H-Pyrazolo[4,3-g]quinazolin-5-amine, N-(3-bromophenyl)- (CA INDEX NAME)



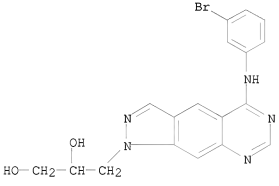
IT 189019-13-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrrolo- and pyrazoloquinazolines as epidermal growth factor receptor inhibitors)
RN 189019-13-4 CAPLUS
CN Glycine, N-[[4-[(3-bromophenyl)amino]-8H-pyrrolo[3,2-g]quinazolin-6-yl]methyl]-N-methyl-, methyl ester (CA INDEX NAME)



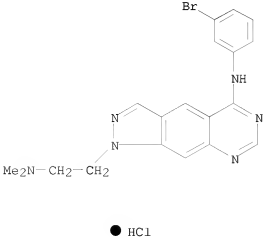
IT 189018-86-8P 189018-87-9P 189018-89-1P
189018-91-5P 189018-92-6P 189018-93-7P
189018-94-8P 189018-95-9P 189018-96-0P
189018-97-1P 189018-98-2P 189018-99-3P
189019-09-8P 189019-10-1P 189019-11-2P
189019-12-3P 189019-14-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of pyrrolo- and pyrazoloquinazolines as epidermal growth factor receptor inhibitors)
RN 189018-86-8 CAPLUS
CN 1H-Pyrazolo[4,3-g]quinazolin-5-amine, N-(3-bromophenyl)-1-methyl- (CA INDEX NAME)



RN 189018-87-9 CAPLUS
CN 1,2-Propanediol, 3-[5-[(3-bromophenyl)amino]-1H-pyrazolo[4,3-g]quinazolin-1-yl]- (CA INDEX NAME)

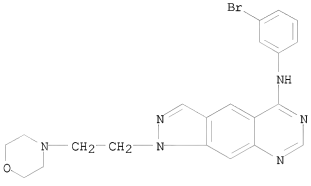


RN 189018-89-1 CAPLUS
CN 1H-Pyrazolo[4,3-g]quinazoline-1-ethanamine, 5-[(3-bromophenyl)amino]-N,N-dimethyl-, hydrochloride (1:1) (CA INDEX NAME)



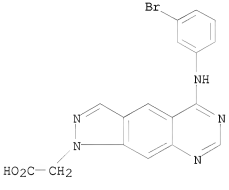
● HCl

RN 189018-91-5 CAPLUS
CN 1H-Pyrazolo[4,3-g]quinazolin-5-amine, N-(3-bromophenyl)-1-[2-(4-morpholinyl)ethyl]-, hydrochloride (1:2) (CA INDEX NAME)

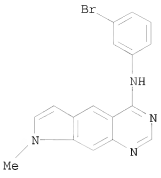


●2 HCl

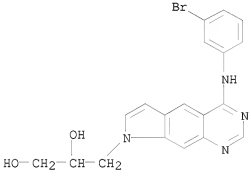
RN 189018-92-6 CAPLUS
CN 1H-Pyrazolo[4,3-g]quinazoline-1-acetic acid, 5-[(3-bromophenyl)amino]- (CA INDEX NAME)



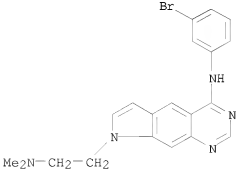
RN 189018-93-7 CAPLUS
CN 8H-Pyrrolo[3,2-g]quinazolin-4-amine, N-(3-bromophenyl)-8-methyl- (CA INDEX NAME)



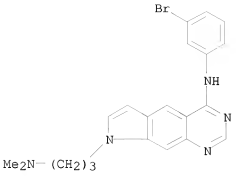
RN 189018-94-8 CAPLUS
CN 1,2-Propanediol, 3-[4-[(3-bromophenyl)amino]-8H-pyrrolo[3,2-g]quinazolin-8-yl]- (CA INDEX NAME)



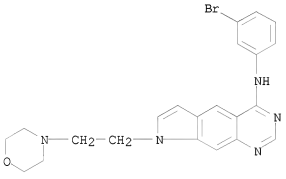
RN 189018-95-9 CAPLUS
CN 8H-Pyrrolo[3,2-g]quinazoline-8-ethanamine, 4-[(3-bromophenyl)amino]-N,N-dimethyl- (CA INDEX NAME)



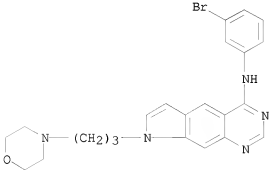
RN 189018-96-0 CAPLUS
CN 8H-Pyrrolo[3,2-g]quinazoline-8-propanamine, 4-[(3-bromophenyl)amino]-N,N-dimethyl- (CA INDEX NAME)



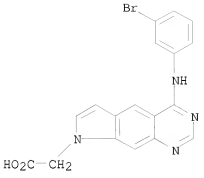
RN 189018-97-1 CAPLUS
CN 8H-Pyrrolo[3,2-g]quinazolin-4-amine,
N-(3-bromophenyl)-8-[2-(4-morpholinyl)ethyl]- (CA INDEX NAME)



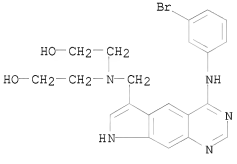
RN 189018-98-2 CAPLUS
CN 8H-Pyrrolo[3,2-g]quinazolin-4-amine,
N-(3-bromophenyl)-8-[3-(4-morpholinyl)propyl]- (CA INDEX NAME)



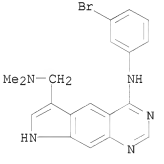
RN 189018-99-3 CAPLUS
CN 8H-Pyrrolo[3,2-g]quinazoline-8-acetic acid, 4-[(3-bromophenyl)amino]- (CA INDEX NAME)



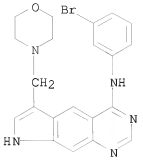
RN 189019-09-8 CAPLUS
CN Ethanol, 2,2'-[[[4-[(3-bromophenyl)amino]-8H-pyrrolo[3,2-g]quinazolin-6-yl]methyl]imino]bis- (CA INDEX NAME)



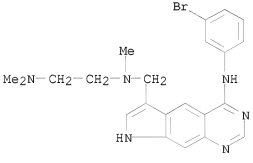
RN 189019-10-1 CAPLUS
CN 8H-Pyrrolo[3,2-g]quinazoline-6-methanamine, 4-[(3-bromophenyl)amino]-N,N-dimethyl- (CA INDEX NAME)



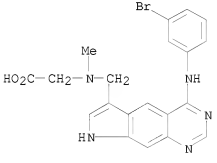
RN 189019-11-2 CAPLUS
CN 8H-Pyrrolo[3,2-g]quinazolin-4-amine, N-(3-bromophenyl)-6-(4-morpholinylmethyl)- (CA INDEX NAME)



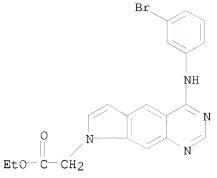
RN 189019-12-3 CAPLUS
CN 1,2-Ethanediamine, N1-[[4-[(3-bromophenyl)amino]-8H-pyrrolo[3,2-g]quinazolin-6-yl]methyl]-N1,N2,N2-trimethyl- (CA INDEX NAME)



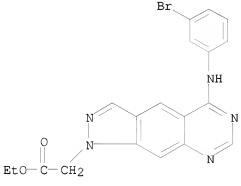
RN 189019-14-5 CAPLUS
CN Glycine, N-[[4-[(3-bromophenyl)amino]-8H-pyrrolo[3,2-g]quinazolin-6-yl]methyl]-N-methyl- (CA INDEX NAME)



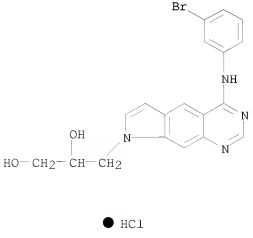
IT 189019-00-9P 189019-01-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrrolo- and pyrazoloquinazolines as epidermal growth factor receptor inhibitors)
RN 189019-00-9 CAPLUS
CN 8H-Pyrrolo[3,2-g]quinazoline-8-acetic acid, 4-[(3-bromophenyl)amino]-, ethyl ester (CA INDEX NAME)



RN 189019-01-0 CAPLUS
CN 1H-Pyrazolo[4,3-g]quinazoline-1-acetic acid, 5-[(3-bromophenyl)amino]-, ethyl ester (CA INDEX NAME)



IT 189019-08-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of pyrrolo- and pyrazoloquinazolines as epidermal growth factor receptor inhibitors)
RN 189019-08-7 CAPLUS
CN 1,2-Propanediol, 3-[4-[(3-bromophenyl)amino]-8H-pyrrolo[3,2-g]quinazolin-8-yl]-, hydrochloride (1:1) (CA INDEX NAME)



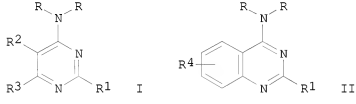
● HCl

OS.CITING REF COUNT: 110 THERE ARE 110 CAPLUS RECORDS THAT CITE THIS RECORD (111 CITINGS)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 38 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1996:580373 CAPLUS
DOCUMENT NUMBER: 125:221864
ORIGINAL REFERENCE NO.: 125:41469a,41472a
TITLE: Preparation of 4-aminopyrimidines and 4-aminoquinazolines
INVENTOR(S): Zielinski, Wojciech; Mazik, Monika
PATENT ASSIGNEE(S): Politechnika Slaska, Pol.
SOURCE: Pol., 5 pp.
CODEN: POXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Polish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PL 169025	B1	19960531	PL 1992-296745	19921124
PRIORITY APPLN. INFO.:			PL 1992-296745	19921124

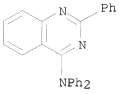
OTHER SOURCE(S): CASREACT 125:221864; MARPAT 125:221864
GI



AB The title compds. [I and II; R = H, alkyl, aryl; R1, R3 = alkyl, aryl; R2 = H, alkyl, (substituted) Ph; R4 = H, alkyl, alkoxy, etc.], useful as potential anticancer agents, antihypertensives, antiviral (HIV-1) agents and fungicides (no data), were prepared by reaction of R5N:C(R1)X [R5 = R2CH:CR3, R4C6H4; X = Cl, C12P(O), etc.] with R2NC.tplbond.N followed by cyclization of the intermediate R5N:CN:C(X)NR2 (III). Refluxing the intermediate III (R5 = R2CH:CR3) in PhMe afforded compds. I while refluxing III (R5 = R4C6H4) in the presence of Lewis acids such as TiCl4 in C6H6 afforded compds. II.

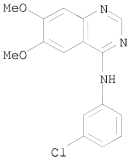
IT 103051-13-4P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of 4-aminopyrimidines and 4-aminoquinazolines)

RN 103051-13-4 CAPLUS
CN 4-Quinazolinamine, N,N,2-triphenyl- (CA INDEX NAME)



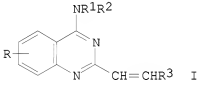
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L5 ANSWER 39 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1996:116898 CAPLUS
DOCUMENT NUMBER: 124:249905
ORIGINAL REFERENCE NO.: 124:45965a,45968a
TITLE: Inhibition of acute lymphoblastic leukemia by a Jak-2 inhibitor
AUTHOR(S): Meydan, Naftaly; Grunberger, Tom; Dadi, Harjit; Shahar, Michal; Arpaia, Enrico; Lapidot, Zvi; Leeder, J. Steven; Freedman, Melvin; Cohen, Amos; et al.
CORPORATE SOURCE: The Hospital for Sick Children, Univ. Toronto, Toronto, M5G 1X8, Can.
SOURCE: Nature (London) (1996), 379(6566), 645-8
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acute lymphoblastic leukemia (ALL) is the most common cancer of childhood. Despite the progress achieved in its treatment, 20% of cases relapse and no longer respond to chemotherapy. The most common phenotype of all cells share surface antigens with very early precursors of B cells and are therefore believed to originate from this lineage. Characterization of the growth requirement of ALL cells indicated that they were dependent on various cytokines, suggesting paracrine and/or autocrine growth regulation. Because many cytokines induce tyrosine phosphorylation in lymphoid progenitor cells, and constitutive tyrosine phosphorylation is commonly observed in B-lineage leukemias, attempts have been made to develop protein tyrosine kinase (PTK) blockers of leukemia cell growth. Here the authors show that leukemic cells from patients in relapse have constitutively activated Jak-2 PTK. Inhibition of Jak-2 activity by a specific tyrosine kinase blocker, AG-490, selectively blocks leukemic cell growth in vitro and in vivo by inducing programmed cell death, with no deleterious effect on normal hematopoiesis. None of the other tyrphostins tested had any activity against leukemic cells.
IT 153436-53-4, AG 1478
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of acute lymphoblastic leukemia by a Jak-2 protein tyrosine kinase inhibitor AG-490 in relation to screening of other tyrphostins)
RN 153436-53-4 CAPLUS
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (CA INDEX NAME)



OS.CITING REF COUNT: 578 THERE ARE 578 CAPLUS RECORDS THAT CITE THIS RECORD (578 CITINGS)

L5 ANSWER 40 OF 40 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 1987:32975 CAPLUS
DOCUMENT NUMBER: 106:32975
ORIGINAL REFERENCE NO.: 106:5531a
TITLE: 4-Amino-2-styrylquinazolines - a new class of antiprotozoal drugs
AUTHOR(S): Moskalenko, N. Yu.; Yakhontov, L. N.; Zhikhareva, G. P.; Pershin, G. N.; Peters, V. V.; Evstratova, M. I.; Mastafanova, L. I.; Rabinovich, S. A.; Maksakovskaya, E. V.; Kulikovskaya, I. M.
CORPORATE SOURCE: Vses. Nauchno-Issled. Khim.-Farm. Inst. im. Ordzhonikidze, Moscow, USSR
SOURCE: Khimiko-Farmatsevticheskii Zhurnal (1986), 20(4), 437-46
CODEN: KHFZAN; ISSN: 0023-1134
DOCUMENT TYPE: Journal
LANGUAGE: Russian
OTHER SOURCE(S): CASREACT 106:32975
GI



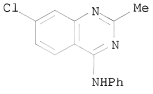
AB 4-Amino-2-styrylquinazolines (I, R = H, 6-OMe, 7-Cl or 6-NO2; NR1R2 = NHCHMe(CH2)3NEt2, Et2N, piperidino or PhNH; and R3 = 4-aminophenyl, 2-nitrophenyl, 4-nitrophenyl, 2-anisyl, 2-(2-nitrofuryl), or halophenyl, etc.,) were prepared by the reaction of the corresponding N-substituted-2-methylquinazolines with suitable aldehydes. Various pharmacol. activities of these compds., e.g., trypanosomicidal, amebicidal, protozoacidal, antimalarial, etc., were determined The LD50 for these compds. are tabulated. Against protozoal infections, 4-(δ-diethylamino-α-methylbutylamino)-2-styrylquinazoline with a p-nitro group in the styrene ring showed the highest activity. Replacement of the nitro group by halogen atoms decreased the protozoacidal activity. The presence of the 4-δ-diethylamino-α-methylbutylamino group in

styrylquinazolines is necessary for exhibiting the antileishmaniasis activity. Other structure-activity correlations are discussed.

IT 57942-23-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with aldehydes)

RN 57942-23-1 CAPLUS

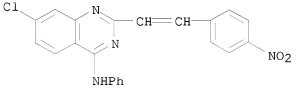
CN 4-Quinazolinamine, 7-chloro-2-methyl-N-phenyl- (CA INDEX NAME)



IT 57942-30-0P 106008-13-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and protozoacidal activity of)

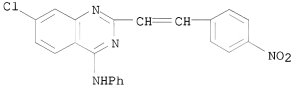
RN 57942-30-0 CAPLUS

CN 4-Quinazolinamine, 7-chloro-2-[2-(4-nitrophenyl)ethenyl]-N-phenyl- (CA INDEX NAME)



RN 106008-13-3 CAPLUS

CN 4-Quinazolinamine, 7-chloro-2-[2-(4-nitrophenyl)ethenyl]-N-phenyl-, hydrochloride (1:1) (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

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(FILE 'HOME' ENTERED AT 17:28:26 ON 17 MAY 2010)

FILE 'REGISTRY' ENTERED AT 17:28:39 ON 17 MAY 2010

L1 STRUCTURE UPLOADED

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L2        59611 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 17:30:00 ON 17 MAY 2010
L3         5362 S L2
L4          495 S L3 NOT PY>2002
L5           40 S L4 AND ((PROTEIN KINASE) OR ANTIVIRAL OR INFECTIO?)

=> log y
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                 XXXXXXXXXXXXXXXXX

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -34.00     -34.00

STN INTERNATIONAL LOGOFF AT 17:35:38 ON 17 MAY 2010
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